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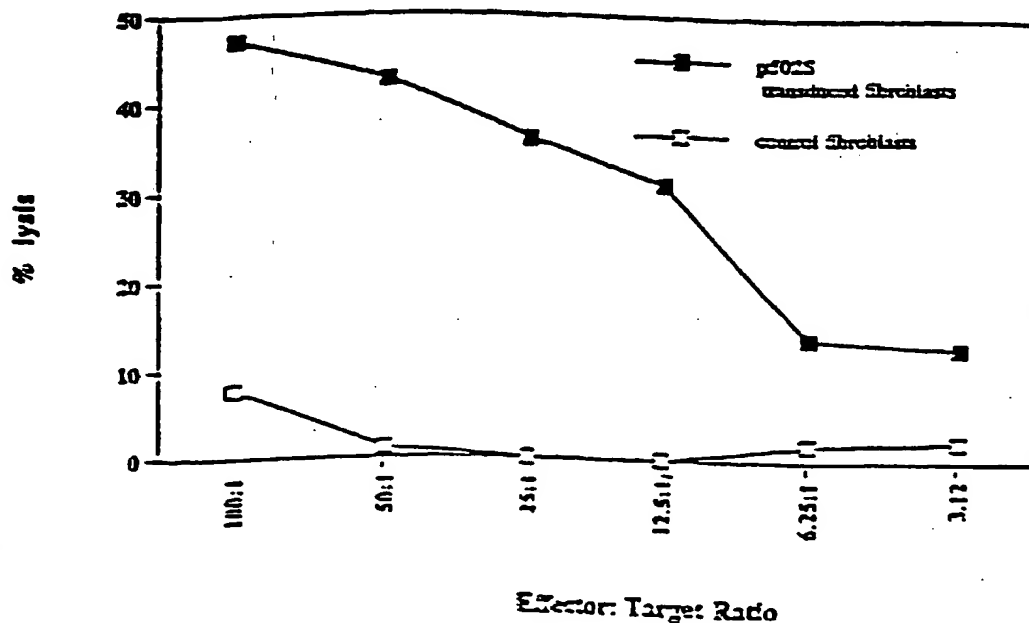
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[Continued on next page]

(54) Title: **COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER**



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.



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## COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

### 5 TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides, comprising at least a portion of a prostate-specific protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides  
10 are useful in pharmaceutical compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of prostate cancer.

### BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although Cancer is a significant health problem throughout the world. Although advances have  
15 been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Prostate cancer is the most common form of cancer among males, with  
20 an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

25 In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA)

and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

## 10 SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375,

381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, under moderately stringent conditions;

5 (e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

10 (f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

15 (g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

20 In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of prostate tissue samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for other normal tissues.

25 The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences  
30 recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383,

477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

In certain preferred embodiments, the polypeptides and/or  
5 polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the  
10 fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-  
15 629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 or 789-791, or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626,  
20 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

25 Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic  
30 applications. Such compositions generally comprise an immunogenic polypeptide or

polynucleotide of the invention and an immunostimulant, such as an adjuvant, together with a physiologically acceptable carrier.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, *e.g.*, vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusion proteins may comprise multiple immunogenic polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating and/or enhancing the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a

patient a pharmaceutical composition as recited above. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for  
5 removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the polypeptide from the sample.

Within related aspects, methods are provided for inhibiting the  
10 development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a  
15 polynucleotide encoding such a polypeptide; and (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for  
20 inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide  
25 comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a prostate cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide of the present invention, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to an inventive polynucleotide, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample an amount of a polynucleotide that  
5 hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as  
10 monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All  
15 references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

#### BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate-specific polypeptide P502S, as compared to control fibroblasts.  
20 The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate-specific polypeptide P502S. In each case, the number of  $\gamma$ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to  
25 fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/*neu*.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release



bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate-specific polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate-specific antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target ratios as indicated.

Figure 7 is a Western blot showing the expression of P501S in baculovirus.

Figure 8 illustrates the results of epitope mapping studies on P501S.

Figure 9 is a schematic representation of the P501S protein showing the location of transmembrane domains and predicted intracellular and extracellular domains.

Figure 10 is a genomic map showing the location of the prostate genes P775P, P704P, B305D, P712P and P774P within the Cat Eye Syndrome region of chromosome 22q11.2.

Figure 11 shows the results of an ELISA assay to determine the specificity of rabbit polyclonal antisera raised against P501S.

SEQ ID NO: 1 is the determined cDNA sequence for F1-13

SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

5 SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16  
SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1  
SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9  
SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4  
SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17  
SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17  
SEQ ID NO: 10 is the determined 3' cDNA sequence for L1-12  
10 SEQ ID NO: 11 is the determined 5' cDNA sequence for L1-12  
SEQ ID NO: 12 is the determined 3' cDNA sequence for N1-1862  
SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862  
SEQ ID NO: 14 is the determined 3' cDNA sequence for J1-13  
SEQ ID NO: 15 is the determined 5' cDNA sequence for J1-13  
SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19  
SEQ ID NO: 17 is the determined 5' cDNA sequence for J1-19  
15 SEQ ID NO: 18 is the determined 3' cDNA sequence for J1-25  
SEQ ID NO: 19 is the determined 5' cDNA sequence for J1-25  
SEQ ID NO: 20 is the determined 5' cDNA sequence for J1-24  
SEQ ID NO: 21 is the determined 3' cDNA sequence for J1-24  
SEQ ID NO: 22 is the determined 5' cDNA sequence for K1-58  
20 SEQ ID NO: 23 is the determined 3' cDNA sequence for K1-58  
SEQ ID NO: 24 is the determined 5' cDNA sequence for K1-63  
SEQ ID NO: 25 is the determined 3' cDNA sequence for K1-63  
SEQ ID NO: 26 is the determined 5' cDNA sequence for L1-4  
SEQ ID NO: 27 is the determined 3' cDNA sequence for L1-4  
25 SEQ ID NO: 28 is the determined 5' cDNA sequence for L1-14  
SEQ ID NO: 29 is the determined 3' cDNA sequence for L1-14  
SEQ ID NO: 30 is the determined 3' cDNA sequence for J1-12  
SEQ ID NO: 31 is the determined 3' cDNA sequence for J1-16  
SEQ ID NO: 32 is the determined 3' cDNA sequence for J1-21  
30 SEQ ID NO: 33 is the determined 3' cDNA sequence for K1-48

SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55  
SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2  
SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6  
SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858  
5 SEQ ID NO: 38 is the determined 3' cDNA sequence for N1-1860  
SEQ ID NO: 39 is the determined 3' cDNA sequence for N1-1861  
SEQ ID NO: 40 is the determined 3' cDNA sequence for N1-1864  
SEQ ID NO: 41 is the determined cDNA sequence for P5  
SEQ ID NO: 42 is the determined cDNA sequence for P8  
10 SEQ ID NO: 43 is the determined cDNA sequence for P9  
SEQ ID NO: 44 is the determined cDNA sequence for P18  
SEQ ID NO: 45 is the determined cDNA sequence for P20  
SEQ ID NO: 46 is the determined cDNA sequence for P29  
SEQ ID NO: 47 is the determined cDNA sequence for P30  
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SEQ ID NO: 52 is the determined cDNA sequence for P42  
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SEQ ID NO: 57 is the determined cDNA sequence for P55  
25 SEQ ID NO: 58 is the determined cDNA sequence for P60  
SEQ ID NO: 59 is the determined cDNA sequence for P64  
SEQ ID NO: 60 is the determined cDNA sequence for P65  
SEQ ID NO: 61 is the determined cDNA sequence for P73  
SEQ ID NO: 62 is the determined cDNA sequence for P75  
30 SEQ ID NO: 63 is the determined cDNA sequence for P76

SEQ ID NO: 64 is the determined cDNA sequence for P79

SEQ ID NO: 65 is the determined cDNA sequence for P84

SEQ ID NO: 66 is the determined cDNA sequence for P68

SEQ ID NO: 67 is the determined cDNA sequence for P80 (also referred

5 to as P704P)

SEQ ID NO: 68 is the determined cDNA sequence for P82

SEQ ID NO: 69 is the determined cDNA sequence for U1-3064

SEQ ID NO: 70 is the determined cDNA sequence for U1-3065

SEQ ID NO: 71 is the determined cDNA sequence for V1-3692

10 SEQ ID NO: 72 is the determined cDNA sequence for 1A-3905

SEQ ID NO: 73 is the determined cDNA sequence for V1-3686

SEQ ID NO: 74 is the determined cDNA sequence for R1-2330

SEQ ID NO: 75 is the determined cDNA sequence for 1B-3976

SEQ ID NO: 76 is the determined cDNA sequence for V1-3679

15 SEQ ID NO: 77 is the determined cDNA sequence for 1G-4736

SEQ ID NO: 78 is the determined cDNA sequence for 1G-4738

SEQ ID NO: 79 is the determined cDNA sequence for 1G-4741

SEQ ID NO: 80 is the determined cDNA sequence for 1G-4744

SEQ ID NO: 81 is the determined cDNA sequence for 1G-4734

20 SEQ ID NO: 82 is the determined cDNA sequence for 1H-4774

SEQ ID NO: 83 is the determined cDNA sequence for 1H-4781

SEQ ID NO: 84 is the determined cDNA sequence for 1H-4785

SEQ ID NO: 85 is the determined cDNA sequence for 1H-4787

SEQ ID NO: 86 is the determined cDNA sequence for 1H-4796

25 SEQ ID NO: 87 is the determined cDNA sequence for 1I-4807

SEQ ID NO: 88 is the determined cDNA sequence for 1I-4810

SEQ ID NO: 89 is the determined cDNA sequence for 1I-4811

SEQ ID NO: 90 is the determined cDNA sequence for 1J-4876

SEQ ID NO: 91 is the determined cDNA sequence for 1K-4884

30 SEQ ID NO: 92 is the determined cDNA sequence for 1K-4896

- SEQ ID NO: 93 is the determined cDNA sequence for 1G-4761  
SEQ ID NO: 94 is the determined cDNA sequence for 1G-4762  
SEQ ID NO: 95 is the determined cDNA sequence for 1H-4766  
SEQ ID NO: 96 is the determined cDNA sequence for 1H-4770  
5 SEQ ID NO: 97 is the determined cDNA sequence for 1H-4771  
SEQ ID NO: 98 is the determined cDNA sequence for 1H-4772  
SEQ ID NO: 99 is the determined cDNA sequence for 1D-4297  
SEQ ID NO: 100 is the determined cDNA sequence for 1D-4309  
SEQ ID NO: 101 is the determined cDNA sequence for 1D.1-4278  
10 SEQ ID NO: 102 is the determined cDNA sequence for 1D-4288  
SEQ ID NO: 103 is the determined cDNA sequence for 1D-4283  
SEQ ID NO: 104 is the determined cDNA sequence for 1D-4304  
SEQ ID NO: 105 is the determined cDNA sequence for 1D-4296  
SEQ ID NO: 106 is the determined cDNA sequence for 1D-4280  
15 SEQ ID NO: 107 is the determined full length cDNA sequence for F1-12  
(also referred to as P504S)  
SEQ ID NO: 108 is the predicted amino acid sequence for F1-12  
SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17  
SEQ ID NO: 110 is the determined full length cDNA sequence for L1-12  
20 (also referred to as P501S)  
SEQ ID NO: 111 is the determined full length cDNA sequence for N1-  
1862 (also referred to as P503S)  
SEQ ID NO: 112 is the predicted amino acid sequence for J1-17  
SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 (also  
25 referred to as P501S)  
SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 (also  
referred to as P503S)  
SEQ ID NO: 115 is the determined cDNA sequence for P89  
SEQ ID NO: 116 is the determined cDNA sequence for P90  
30 SEQ ID NO: 117 is the determined cDNA sequence for P92

SEQ ID NO: 118 is the determined cDNA sequence for P95  
SEQ ID NO: 119 is the determined cDNA sequence for P98  
SEQ ID NO: 120 is the determined cDNA sequence for P102  
SEQ ID NO: 121 is the determined cDNA sequence for P110  
5 SEQ ID NO: 122 is the determined cDNA sequence for P111  
SEQ ID NO: 123 is the determined cDNA sequence for P114  
SEQ ID NO: 124 is the determined cDNA sequence for P115  
SEQ ID NO: 125 is the determined cDNA sequence for P116  
SEQ ID NO: 126 is the determined cDNA sequence for P124  
10 SEQ ID NO: 127 is the determined cDNA sequence for P126  
SEQ ID NO: 128 is the determined cDNA sequence for P130  
SEQ ID NO: 129 is the determined cDNA sequence for P133  
SEQ ID NO: 130 is the determined cDNA sequence for P138  
SEQ ID NO: 131 is the determined cDNA sequence for P143  
15 SEQ ID NO: 132 is the determined cDNA sequence for P151  
SEQ ID NO: 133 is the determined cDNA sequence for P156  
SEQ ID NO: 134 is the determined cDNA sequence for P157  
SEQ ID NO: 135 is the determined cDNA sequence for P166  
SEQ ID NO: 136 is the determined cDNA sequence for P176  
20 SEQ ID NO: 137 is the determined cDNA sequence for P178  
SEQ ID NO: 138 is the determined cDNA sequence for P179  
SEQ ID NO: 139 is the determined cDNA sequence for P185  
SEQ ID NO: 140 is the determined cDNA sequence for P192  
SEQ ID NO: 141 is the determined cDNA sequence for P201  
25 SEQ ID NO: 142 is the determined cDNA sequence for P204  
SEQ ID NO: 143 is the determined cDNA sequence for P208  
SEQ ID NO: 144 is the determined cDNA sequence for P211  
SEQ ID NO: 145 is the determined cDNA sequence for P213  
SEQ ID NO: 146 is the determined cDNA sequence for P219  
30 SEQ ID NO: 147 is the determined cDNA sequence for P237

5 SEQ ID NO: 148 is the determined cDNA sequence for P239  
SEQ ID NO: 149 is the determined cDNA sequence for P248  
SEQ ID NO: 150 is the determined cDNA sequence for P251  
SEQ ID NO: 151 is the determined cDNA sequence for P255  
SEQ ID NO: 152 is the determined cDNA sequence for P256  
SEQ ID NO: 153 is the determined cDNA sequence for P259  
SEQ ID NO: 154 is the determined cDNA sequence for P260  
SEQ ID NO: 155 is the determined cDNA sequence for P263  
SEQ ID NO: 156 is the determined cDNA sequence for P264  
10 SEQ ID NO: 157 is the determined cDNA sequence for P266  
SEQ ID NO: 158 is the determined cDNA sequence for P270  
SEQ ID NO: 159 is the determined cDNA sequence for P272  
SEQ ID NO: 160 is the determined cDNA sequence for P278  
SEQ ID NO: 161 is the determined cDNA sequence for P105  
15 SEQ ID NO: 162 is the determined cDNA sequence for P107  
SEQ ID NO: 163 is the determined cDNA sequence for P137  
SEQ ID NO: 164 is the determined cDNA sequence for P194  
SEQ ID NO: 165 is the determined cDNA sequence for P195  
SEQ ID NO: 166 is the determined cDNA sequence for P196  
20 SEQ ID NO: 167 is the determined cDNA sequence for P220  
SEQ ID NO: 168 is the determined cDNA sequence for P234  
SEQ ID NO: 169 is the determined cDNA sequence for P235  
SEQ ID NO: 170 is the determined cDNA sequence for P243  
SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1  
25 SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1  
SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2  
SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6  
SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13  
SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13  
30 SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14

SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14  
SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-

4736

SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-

5 4738

SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-

4741

SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-

4744

10

SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-

4774

SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-

4781

SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-

15 4785

SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-

4787

SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-

4796

20

SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-

4807

SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810

SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811

SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-

25 4876

SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-

4884

SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-

4896



SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-  
4761

SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-  
4762

5 SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-  
4766

SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770  
SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771  
SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-  
10 4772

SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-  
4309

SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-  
4278

15 SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-  
4288

SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-  
4283

SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-  
20 4304

SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-  
4296

SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-  
4280

25 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd  
SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con  
SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev  
SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd  
SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev  
30 SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd

SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev  
SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd  
SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev  
SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd  
5 SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev  
SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd  
SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev  
SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev  
SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd  
10 SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev  
SEQ ID NO: 223 is the determined cDNA sequence for P509S  
SEQ ID NO: 224 is the determined cDNA sequence for P510S  
SEQ ID NO: 225 is the determined cDNA sequence for P703DE5  
SEQ ID NO: 226 is the determined cDNA sequence for 9-A11  
15 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6  
SEQ ID NO: 228 is the determined cDNA sequence for 8-H7  
SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13  
SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14  
SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23  
20 SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24  
SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25  
SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30  
SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34  
SEQ ID NO: 236 is the determined cDNA sequence for PTPN35  
25 SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36  
SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38  
SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39  
SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40  
SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41  
30 SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42

SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45  
SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46  
SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51  
SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56  
5 SEQ ID NO: 247 is the determined cDNA sequence for PTPN64  
SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65  
SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67  
SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76  
SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84  
10 SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85  
SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86  
SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87  
SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88  
SEQ ID NO: 256 is the determined cDNA sequence for JP1F1  
15 SEQ ID NO: 257 is the determined cDNA sequence for JP1F2  
SEQ ID NO: 258 is the determined cDNA sequence for JP1C2  
SEQ ID NO: 259 is the determined cDNA sequence for JP1B1  
SEQ ID NO: 260 is the determined cDNA sequence for JP1B2  
SEQ ID NO: 261 is the determined cDNA sequence for JP1D3  
20 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4  
SEQ ID NO: 263 is the determined cDNA sequence for JP1F5  
SEQ ID NO: 264 is the determined cDNA sequence for JP1E6  
SEQ ID NO: 265 is the determined cDNA sequence for JP1D6  
SEQ ID NO: 266 is the determined cDNA sequence for JP1B5  
25 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6  
SEQ ID NO: 268 is the determined cDNA sequence for JP1E8  
SEQ ID NO: 269 is the determined cDNA sequence for JP1D7  
SEQ ID NO: 270 is the determined cDNA sequence for JP1D9  
SEQ ID NO: 271 is the determined cDNA sequence for JP1C10  
30 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9

5 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12  
SEQ ID NO: 274 is the determined cDNA sequence for JP1E12  
SEQ ID NO: 275 is the determined cDNA sequence for JP1D11  
SEQ ID NO: 276 is the determined cDNA sequence for JP1C11  
SEQ ID NO: 277 is the determined cDNA sequence for JP1C12  
SEQ ID NO: 278 is the determined cDNA sequence for JP1B12  
SEQ ID NO: 279 is the determined cDNA sequence for JP1A12  
SEQ ID NO: 280 is the determined cDNA sequence for JP8G2  
10 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1  
SEQ ID NO: 282 is the determined cDNA sequence for JP8H2  
SEQ ID NO: 283 is the determined cDNA sequence for JP8A3  
SEQ ID NO: 284 is the determined cDNA sequence for JP8A4  
SEQ ID NO: 285 is the determined cDNA sequence for JP8C3  
SEQ ID NO: 286 is the determined cDNA sequence for JP8G4  
15 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6  
SEQ ID NO: 288 is the determined cDNA sequence for JP8D6  
SEQ ID NO: 289 is the determined cDNA sequence for JP8F5  
SEQ ID NO: 290 is the determined cDNA sequence for JP8A8  
SEQ ID NO: 291 is the determined cDNA sequence for JP8C7  
20 SEQ ID NO: 292 is the determined cDNA sequence for JP8D7  
SEQ ID NO: 293 is the determined cDNA sequence for P8D8  
SEQ ID NO: 294 is the determined cDNA sequence for JP8E7  
SEQ ID NO: 295 is the determined cDNA sequence for JP8F8  
SEQ ID NO: 296 is the determined cDNA sequence for JP8G8  
25 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10  
SEQ ID NO: 298 is the determined cDNA sequence for JP8C10  
SEQ ID NO: 299 is the determined cDNA sequence for JP8E9  
SEQ ID NO: 300 is the determined cDNA sequence for JP8E10  
SEQ ID NO: 301 is the determined cDNA sequence for JP8F9  
30 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9

- SEQ ID NO: 303 is the determined cDNA sequence for JP8C12  
SEQ ID NO: 304 is the determined cDNA sequence for JP8E11  
SEQ ID NO: 305 is the determined cDNA sequence for JP8E12  
SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12  
5 SEQ ID NO: 307 is the determined cDNA sequence for P711P  
SEQ ID NO: 308 is the determined cDNA sequence for P712P  
SEQ ID NO: 309 is the determined cDNA sequence for CLONE23  
SEQ ID NO: 310 is the determined cDNA sequence for P774P  
SEQ ID NO: 311 is the determined cDNA sequence for P775P  
10 SEQ ID NO: 312 is the determined cDNA sequence for P715P  
SEQ ID NO: 313 is the determined cDNA sequence for P710P  
SEQ ID NO: 314 is the determined cDNA sequence for P767P  
SEQ ID NO: 315 is the determined cDNA sequence for P768P  
SEQ ID NO: 316-325 are the determined cDNA sequences of previously  
15 isolated genes  
SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5  
SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5  
SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26  
SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26  
20 SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23  
SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23  
SEQ ID NO: 332 is the determined full length cDNA sequence for  
P509S  
SEQ ID NO: 333 is the determined extended cDNA sequence for P707P  
25 (also referred to as 11-C9)  
SEQ ID NO: 334 is the determined cDNA sequence for P714P  
SEQ ID NO: 335 is the determined cDNA sequence for P705P (also  
referred to as 9-F3)  
SEQ ID NO: 336 is the predicted amino acid sequence for P705P  
30 SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

- SEQ ID NO: 338 is the amino acid sequence of the peptide p5
- SEQ ID NO: 339 is the predicted amino acid sequence of P509S
- SEQ ID NO: 340 is the determined cDNA sequence for P778P
- SEQ ID NO: 341 is the determined cDNA sequence for P786P
- 5 SEQ ID NO: 342 is the determined cDNA sequence for P789P
- SEQ ID NO: 343 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens MM46 mRNA
- SEQ ID NO: 344 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA
- 10 SEQ ID NO: 345 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens mRNA for E-cadherin
- SEQ ID NO: 346 is the determined cDNA sequence for a clone showing  
homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase  
(SHMT)
- 15 SEQ ID NO: 347 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens natural resistance-associated macrophage protein2  
(NRAMP2)
- SEQ ID NO: 348 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)
- 20 SEQ ID NO: 349 is the determined cDNA sequence for a clone showing  
homology to Human mRNA for proteosome subunit p40
- SEQ ID NO: 350 is the determined cDNA sequence for P777P
- SEQ ID NO: 351 is the determined cDNA sequence for P779P
- SEQ ID NO: 352 is the determined cDNA sequence for P790P
- 25 SEQ ID NO: 353 is the determined cDNA sequence for P784P
- SEQ ID NO: 354 is the determined cDNA sequence for P776P
- SEQ ID NO: 355 is the determined cDNA sequence for P780P
- SEQ ID NO: 356 is the determined cDNA sequence for P544S
- SEQ ID NO: 357 is the determined cDNA sequence for P745S
- 30 SEQ ID NO: 358 is the determined cDNA sequence for P782P

- SEQ ID NO: 359 is the determined cDNA sequence for P783P  
SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984  
SEQ ID NO: 361 is the determined cDNA sequence for P787P.  
SEQ ID NO: 362 is the determined cDNA sequence for P788P  
5 SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994  
SEQ ID NO: 364 is the determined cDNA sequence for P781P  
SEQ ID NO: 365 is the determined cDNA sequence for P785P  
SEQ ID NO: 366-375 are the determined cDNA sequences for splice  
variants of B305D.
- 10 SEQ ID NO: 376 is the predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 366.  
SEQ ID NO: 377 is the predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 372.  
SEQ ID NO: 378 is the predicted amino acid sequence encoded by the  
15 sequence of SEQ ID NO: 373.  
SEQ ID NO: 379 is the predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 374.  
SEQ ID NO: 380 is the predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 375.
- 20 SEQ ID NO: 381 is the determined cDNA sequence for B716P.  
SEQ ID NO: 382 is the determined full-length cDNA sequence for  
P711P.  
SEQ ID NO: 383 is the predicted amino acid sequence for P711P.  
SEQ ID NO: 384 is the cDNA sequence for P1000C.  
25 SEQ ID NO: 385 is the cDNA sequence for CGI-82.  
SEQ ID NO: 386 is the cDNA sequence for 23320.  
SEQ ID NO: 387 is the cDNA sequence for CGI-69.  
SEQ ID NO: 388 is the cDNA sequence for L-iditol-2-dehydrogenase.  
SEQ ID NO: 389 is the cDNA sequence for 23379.  
30 SEQ ID NO: 390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

5 SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor

PDEF.

10 SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

15 SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553 (also known as

P1020C).

20 SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567.

SEQ ID NO:412 is the cDNA sequence for 22568.

25 SEQ ID NO:413 is the cDNA sequence for 22570.

SEQ ID NO:414 is the cDNA sequence for 22571.

SEQ ID NO:415 is the cDNA sequence for 22572.

SEQ ID NO:416 is the cDNA sequence for 22573.

SEQ ID NO:417 is the cDNA sequence for 22573.

30 SEQ ID NO:418 is the cDNA sequence for 22575.



SEQ ID NO:419 is the cDNA sequence for 22580.  
SEQ ID NO:420 is the cDNA sequence for 22581.  
SEQ ID NO:421 is the cDNA sequence for 22582.  
SEQ ID NO:422 is the cDNA sequence for 22583.  
5 SEQ ID NO:423 is the cDNA sequence for 22584.  
SEQ ID NO:424 is the cDNA sequence for 22585.  
SEQ ID NO:425 is the cDNA sequence for 22586.  
SEQ ID NO:426 is the cDNA sequence for 22587.  
SEQ ID NO:427 is the cDNA sequence for 22588.  
10 SEQ ID NO:428 is the cDNA sequence for 22589.  
SEQ ID NO:429 is the cDNA sequence for 22590.  
SEQ ID NO:430 is the cDNA sequence for 22591.  
SEQ ID NO:431 is the cDNA sequence for 22592.  
SEQ ID NO:432 is the cDNA sequence for 22593.  
15 SEQ ID NO:433 is the cDNA sequence for 22594.  
SEQ ID NO:434 is the cDNA sequence for 22595.  
SEQ ID NO:435 is the cDNA sequence for 22596.  
SEQ ID NO:436 is the cDNA sequence for 22847.  
SEQ ID NO:437 is the cDNA sequence for 22848.  
20 SEQ ID NO:438 is the cDNA sequence for 22849.  
SEQ ID NO:439 is the cDNA sequence for 22851.  
SEQ ID NO:440 is the cDNA sequence for 22852.  
SEQ ID NO:441 is the cDNA sequence for 22853.  
SEQ ID NO:442 is the cDNA sequence for 22854.  
25 SEQ ID NO:443 is the cDNA sequence for 22855.  
SEQ ID NO:444 is the cDNA sequence for 22856.  
SEQ ID NO:445 is the cDNA sequence for 22857.  
SEQ ID NO:446 is the cDNA sequence for 23601.  
SEQ ID NO:447 is the cDNA sequence for 23602.  
30 SEQ ID NO:448 is the cDNA sequence for 23605.

- SEQ ID NO:449 is the cDNA sequence for 23606.  
SEQ ID NO:450 is the cDNA sequence for 23612.  
SEQ ID NO:451 is the cDNA sequence for 23614.  
SEQ ID NO:452 is the cDNA sequence for 23618.  
5 SEQ ID NO:453 is the cDNA sequence for 23622.  
SEQ ID NO:454 is the cDNA sequence for folate hydrolase.  
SEQ ID NO:455 is the cDNA sequence for LIM protein.  
SEQ ID NO:456 is the cDNA sequence for a known gene.  
SEQ ID NO:457 is the cDNA sequence for a known gene.  
10 SEQ ID NO:458 is the cDNA sequence for a previously identified gene.  
SEQ ID NO:459 is the cDNA sequence for 23045.  
SEQ ID NO:460 is the cDNA sequence for 23032.  
SEQ ID NO:461 is the cDNA sequence for clone 23054.  
SEQ ID NO:462-467 are cDNA sequences for known genes.  
15 SEQ ID NO:468-471 are cDNA sequences for P710P.  
SEQ ID NO:472 is a cDNA sequence for P1001C.  
SEQ ID NO: 473 is the determined cDNA sequence for a first splice  
variant of P775P (referred to as 27505).  
SEQ ID NO: 474 is the determined cDNA sequence for a second splice  
20 variant of P775P (referred to as 19947).  
SEQ ID NO: 475 is the determined cDNA sequence for a third splice  
variant of P775P (referred to as 19941).  
SEQ ID NO: 476 is the determined cDNA sequence for a fourth splice  
variant of P775P (referred to as 19937).  
25 SEQ ID NO: 477 is a first predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 474.  
SEQ ID NO: 478 is a second predicted amino acid sequence encoded by  
the sequence of SEQ ID NO: 474.  
SEQ ID NO: 479 is the predicted amino acid sequence encoded by the  
30 sequence of SEQ ID NO: 475.

SEQ ID NO: 480 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 481 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

5           SEQ ID NO: 482 is a third predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 483 is a fourth predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

10           SEQ ID NO: 484 is the first 30 amino acids of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 485 is the PCR primer AW025.

SEQ ID NO: 486 is the PCR primer AW003.

SEQ ID NO: 487 is the PCR primer AW027.

SEQ ID NO: 488 is the PCR primer AW026.

15           SEQ ID NO: 489-501 are peptides employed in epitope mapping studies.

SEQ ID NO: 502 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody 20D4.

SEQ ID NO: 503 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody JA1.

20           SEQ ID NO: 504 & 505 are peptides employed in epitope mapping studies.

SEQ ID NO: 506 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 8H2.

25           SEQ ID NO: 507 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 7H8.

SEQ ID NO: 508 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 2D4.

SEQ ID NO: 509-522 are peptides employed in epitope mapping studies.

30           SEQ ID NO: 523 is a mature form of P703P used to raise antibodies against P703P.

SEQ ID NO: 524 is the putative full-length cDNA sequence of P703P.

SEQ ID NO: 525 is the predicted amino acid sequence encoded by SEQ ID NO: 524.

SEQ ID NO: 526 is the full-length cDNA sequence for P790P.

5 SEQ ID NO: 527 is the predicted amino acid sequence for P790P.

SEQ ID NO: 528 & 529 are PCR primers.

SEQ ID NO: 530 is the cDNA sequence of a splice variant of SEQ ID NO: 366.

10 SEQ ID NO: 531 is the cDNA sequence of the open reading frame of SEQ ID NO: 530.

SEQ ID NO: 532 is the predicted amino acid encoded by the sequence of SEQ ID NO: 531.

SEQ ID NO: 533 is the DNA sequence of a putative ORF of P775P.

15 ID NO: 533. SEQ ID NO: 534 is the predicted amino acid sequence encoded by SEQ ID NO: 533.

SEQ ID NO: 535 is a first full-length cDNA sequence for P510S.

SEQ ID NO: 536 is a second full-length cDNA sequence for P510S.

20 ID NO: 535. SEQ ID NO: 537 is the predicted amino acid sequence encoded by SEQ ID NO: 535.

SEQ ID NO: 538 is the predicted amino acid sequence encoded by SEQ ID NO: 536.

SEQ ID NO: 539 is the peptide P501S-370.

SEQ ID NO: 540 is the peptide P501S-376.

25 SEQ ID NO: 541-551 are epitopes of P501S.

SEQ ID NO: 552 is an extended cDNA sequence for P712P.

SEQ ID NO: 553-568 are the amino acid sequences encoded by predicted open reading frames within SEQ ID NO: 552.

SEQ ID NO: 569 is an extended cDNA sequence for P776P.

30 of P776P referred to as contig 6. SEQ ID NO: 570 is the determined cDNA sequence for a splice variant

SEQ ID NO: 571 is the determined cDNA sequence for a splice variant of P776P referred to as contig 7.

SEQ ID NO: 572 is the determined cDNA sequence for a splice variant of P776P referred to as contig 14.

5        SEQ ID NO: 573 is the amino acid sequence encoded by a first predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 574 is the amino acid sequence encoded by a second predicted ORF of SEQ ID NO: 570.

10       SEQ ID NO: 575 is the amino acid sequence encoded by a predicted ORF of SEQ ID NO: 571.

SEQ ID NO: 576-586 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 569.

SEQ ID NO: 587 is a DNA consensus sequence of the sequences of P767P and P777P.

15       SEQ ID NO: 588-590 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 587.

SEQ ID NO: 591 is an extended cDNA sequence for P1020C.

SEQ ID NO: 592 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: P1020C.

20       SEQ ID NO: 593 is a splice variant of P775P referred to as 50748.

SEQ ID NO: 594 is a splice variant of P775P referred to as 50717.

SEQ ID NO: 595 is a splice variant of P775P referred to as 45985.

SEQ ID NO: 596 is a splice variant of P775P referred to as 38769.

SEQ ID NO: 597 is a splice variant of P775P referred to as 37922.

25       SEQ ID NO: 598 is a splice variant of P510S referred to as 49274.

SEQ ID NO: 599 is a splice variant of P510S referred to as 39487.

SEQ ID NO: 600 is a splice variant of P504S referred to as 5167.16.

SEQ ID NO: 601 is a splice variant of P504S referred to as 5167.1.

SEQ ID NO: 602 is a splice variant of P504S referred to as 5163.46.

30       SEQ ID NO: 603 is a splice variant of P504S referred to as 5163.42.

SEQ ID NO: 604 is a splice variant of P504S referred to as 5163.34.

SEQ ID NO: 605 is a splice variant of P504S referred to as 5163.17.

SEQ ID NO: 606 is a splice variant of P501S referred to as 10640.

SEQ ID NO: 607-615 are the sequences of PCR primers.

5        SEQ ID NO: 616 is the determined cDNA sequence of a fusion of P703P  
and PSA.

SEQ ID NO: 617 is the amino acid sequence of the fusion of P703P and  
PSA.

SEQ ID NO: 618 is the cDNA sequence of the gene DD3.

10        SEQ ID NO: 619 is an extended cDNA sequence for P714P.

SEQ ID NO: 620-622 are the cDNA sequences for splice variants of  
P704P.

SEQ ID NO: 623 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-14.

15        SEQ ID NO: 624 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-12.

SEQ ID NO: 625 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-10.

20        SEQ ID NO: 626 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-6.

SEQ ID NO: 627 is the amino acid sequence encoded by SEQ ID NO:  
626.

SEQ ID NO: 628 is a first amino acid sequence encoded by SEQ ID NO:  
623.

25        SEQ ID NO: 629 is a second amino acid sequence encoded by SEQ ID  
NO: 623.

SEQ ID NO: 630 is a first full-length cDNA sequence for prostate-  
specific transglutaminase gene (also referred to herein as P558S).

30        SEQ ID NO: 631 is a second full-length cDNA sequence for prostate-  
specific transglutaminase gene.

SEQ ID NO: 632 is the amino acid sequence encoded by the sequence of SEQ ID NO: 630.

SEQ ID NO: 633 is the amino acid sequence encoded by the sequence of SEQ ID NO: 631.

5 SEQ ID NO: 634 is the full-length cDNA sequence for P788P.

SEQ ID NO: 635 is the amino acid sequence encoded by SEQ ID NO: 634.

SEQ ID NO: 636 is the determined cDNA sequence for a polymorphic variant of P788P.

10 SEQ ID NO: 637 is the amino acid sequence encoded by SEQ ID NO: 636.

SEQ ID NO: 638 is the amino acid sequence of peptide 4 from P703P.

SEQ ID NO: 639 is the cDNA sequence that encodes peptide 4 from P703P.

15 SEQ ID NO: 640-655 are cDNA sequences encoding epitopes of P703P.

SEQ ID NO: 656-671 are the amino acid sequences of epitopes of P703P.

SEQ ID NO: 672 and 673 are PCR primers.

20 SEQ ID NO: 674 is the cDNA sequence encoding an N-terminal portion of P788P expressed in *E. coli*.

SEQ ID NO: 675 is the amino acid sequence of the N-terminal portion of P788P expressed in *E. coli*.

SEQ ID NO: 676 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

25 SEQ ID NO: 677 and 678 are PCR primers.

SEQ ID NO: 679 is the cDNA sequence for the Ra12-P510S-C construct.

SEQ ID NO: 680 is the cDNA sequence for the P510S-C construct.

SEQ ID NO: 681 is the cDNA sequence for the P510S-E3 construct.

SEQ ID NO: 682 is the amino acid sequence for the Ra12-P510S-C construct.

SEQ ID NO: 683 is the amino acid sequence for the P510S-C construct.

SEQ ID NO: 684 is the amino acid sequence for the P510S-E3 construct.

5 SEQ ID NO: 685-690 are PCR primers.

SEQ ID NO: 691 is the cDNA sequence of the construct Ra12-P775P-ORF3.

SEQ ID NO: 692 is the amino acid sequence of the construct Ra12-P775P-ORF3.

10 SEQ ID NO: 693 and 694 are PCR primers.

SEQ ID NO: 695 is the determined amino acid sequence for a P703P His tag fusion protein.

SEQ ID NO: 696 is the determined cDNA sequence for a P703P His tag fusion protein.

15 SEQ ID NO: 697 and 698 are PCR primers.

SEQ ID NO: 699 is the determined amino acid sequence for a P705P His tag fusion protein.

SEQ ID NO: 700 is the determined cDNA sequence for a P705P His tag fusion protein.

20 SEQ ID NO: 701 and 702 are PCR primers.

SEQ ID NO: 703 is the determined amino acid sequence for a P711P His tag fusion protein.

SEQ ID NO: 704 is the determined cDNA sequence for a P711P His tag fusion protein.

25 SEQ ID NO: 705 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 706 and 707 are PCR primers.

SEQ ID NO: 708 is the determined cDNA sequence for the construct Ra12-P501S-E2.



SEQ ID NO: 709 is the determined amino acid sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 710 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 711 is the DNA sequence encoding SEQ ID NO: 710.

5 SEQ ID NO: 712 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 713 is the DNA sequence encoding SEQ ID NO: 712.

SEQ ID NO: 714 is a peptide employed in epitope mapping studies.

SEQ ID NO: 715 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 716 is the DNA sequence encoding SEQ ID NO: 715.

10 SEQ ID NO: 717-719 are the amino acid sequences for CD4 epitopes of P501S.

SEQ ID NO: 720-722 are the DNA sequences encoding the sequences of SEQ ID NO: 717-719.

15 SEQ ID NO: 723-734 are the amino acid sequences for putative CTL epitopes of P703P.

SEQ ID NO: 735 is the full-length cDNA sequence for P789P.

SEQ ID NO: 736 is the amino acid sequence encoded by SEQ ID NO: 735.

20 SEQ ID NO: 737 is the determined full-length cDNA sequence for the splice variant of P776P referred to as contig 6.

SEQ ID NO: 738-739 are determined full-length cDNA sequences for the splice variant of P776P referred to as contig 7.

SEQ ID NO: 740-744 are amino acid sequences encoded by SEQ ID NO: 737.

25 SEQ ID NO: 745-750 are amino acid sequences encoded by the splice variant of P776P referred to as contig 7.

SEQ ID NO: 751 is the full-length cDNA sequence for human transmembrane protease serine 2.

30 SEQ ID NO: 752 is the amino acid sequence encoded by SEQ ID NO: 751.

SEQ ID NO: 753 is the cDNA sequence encoding the first 209 amino acids of human transmembrane protease serine 2.

SEQ ID NO: 754 is the first 209 amino acids of human transmembrane protease serine 2,

5           SEQ ID NO: 755 is the amino acid sequence of peptide 296-322 of P501S.

SEQ ID NO: 756-759 are PCR primers.

SEQ ID NO: 760 is the determined cDNA sequence of the Vb chain of a T cell receptor for the P501S-specific T cell clone 4E5.

10           SEQ ID NO: 761 is the determined cDNA sequence of the Va chain of a T cell receptor for the P501S-specific T cell clone 4E5.

SEQ ID NO: 762 is the amino acid sequence encoded by SEQ ID NO 760.

15           SEQ ID NO: 763 is the amino acid sequence encoded by SEQ ID NO 761.

SEQ ID NO: 764 is the full-length open reading frame for P768P including stop codon.

SEQ ID NO: 765 is the full-length open reading frame for P768P without stop codon.

20           SEQ ID NO: 766 is the amino acid sequence encoded by SEQ ID NO: 765.

SEQ ID NO: 767-772 are the amino acid sequences for predicted domains of P768P.

SEQ ID NO: 773 is the full-length cDNA sequence of P835P.

25           SEQ ID NO: 774 is the cDNA sequence of the previously identified clone FLJ13581.

SEQ ID NO: 775 is the cDNA sequence of the open reading frame for P835P with stop codon.

30           SEQ ID NO: 776 is the cDNA sequence of the open reading frame for P835P without stop codon.

SEQ ID NO: 777 is the full-length amino acid sequence for P835P.

SEQ ID NO: 778-785 are the amino acid sequences of extracellular and intracellular domains of P835P.

SEQ ID NO: 786 is the full-length cDNA sequence for P1000C.

5 SEQ ID NO: 787 is the cDNA sequence of the open reading frame for P1000C, including stop codon.

SEQ ID NO: 788 is the cDNA sequence of the open reading frame for P1000C, without stop codon.

SEQ ID NO: 789 is the full-length amino acid sequence for P1000C.

10 SEQ ID NO: 790 is amino acids 1-100 of SEQ ID NO: 789.

SEQ ID NO: 791 is amino acids 100-492 of SEQ ID NO: 789.

SEQ ID NO: 792 is the amino acid sequence of an  $\alpha$  prepro-P501S recombinant protein.

## 15 DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly prostate cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such  
20 polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (e.g., T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of  
25 the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, e.g., Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid

Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

All publications, patents and patent applications cited herein, whether  
5 supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms  
"a," "an" and "the" include plural references unless the content clearly dictates  
otherwise.

#### Polypeptide Compositions

10 As used herein, the term "polypeptide" is used in its conventional  
meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a  
specific length of the product; thus, peptides, oligopeptides, and proteins are included  
within the definition of polypeptide, and such terms may be used interchangeably herein  
unless specifically indicated otherwise. This term also does not refer to or exclude post-  
15 expression modifications of the polypeptide, for example, glycosylations, acetylations,  
phosphorylations and the like, as well as other modifications known in the art, both  
naturally occurring and non-naturally occurring. A polypeptide may be an entire  
protein, or a subsequence thereof. Particular polypeptides of interest in the context of  
this invention are amino acid subsequences comprising epitopes, *i.e.*, antigenic  
20 determinants substantially responsible for the immunogenic properties of a polypeptide  
and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise  
those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111,  
115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382  
25 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-  
626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739,  
751, 753, 764, 765, 773-776 and 786-788, or a sequence that hybridizes under  
moderately stringent conditions, or, alternatively, under highly stringent conditions, to a  
polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175,

177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788. In specific embodiments, the polypeptides of the invention  
5 comprise amino acid sequences as set forth in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

10 The polypeptides of the present invention are sometimes herein referred to as prostate-specific proteins or prostate-specific polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in prostate tissue samples. Thus, a "prostate-specific polypeptide" or "prostate-specific protein," refers generally to a polypeptide sequence of the present  
15 invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of prostate tissue samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of prostate tissue samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in other  
20 normal tissues, as determined using a representative assay provided herein. A prostate-specific polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

In certain preferred embodiments, the polypeptides of the invention are  
25 immunogenic, i.e., they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with prostate cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory*  
30 *Manual*, Cold Spring Harbor Laboratory, 1988. In one illustrative example, a

polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

5           As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.*, specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide.

10   Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they

15   specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

          In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that

20   is not substantially less than the reactivity of the full-length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that

25   have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

          In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain

30   has been deleted. Other illustrative immunogenic portions will contain a small N-

and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells and/or antibodies generated against a polypeptide of the invention, particularly a  
5 polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies  
10 that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide composition set forth herein, such as those set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-  
380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568,  
20 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-  
375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591,  
25 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%,  
30 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95 %, 96%, 97%, 98%, or 99% or more identity

(determined as described below), along its length, to a polypeptide sequence set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provided by the present invention are immunologically reactive with an antibody and/or T-cell that reacts with a full-length polypeptide specifically set forth herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, e.g., with immunogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or



even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydrophatic index of amino acids may be considered. The importance of the hydrophatic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydrophatic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydrophatic index on the basis of its

hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5);  
5 glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are  
10 within  $\pm 2$  is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of  
15 its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0  $\pm$  1); glutamate (+3.0  $\pm$  1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5  $\pm$  1); alanine (-0.5); histidine (-0.5); cysteine  
20 (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within  $\pm 2$   
25 is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that  
30 take various of the foregoing characteristics into consideration are well known to those

of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of  
5 flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

10 Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values  
15 include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a  
20 preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

25 As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For  
30 example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

- Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics

Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known

tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al.,

*Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to  
5 separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and  
10 transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus,  
15 tuberculosis and hepatitis proteins (*see, for example, Stoute et al. New Engl. J. Med.*, 336:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a *Mycobacterium* sp., such as a *Mycobacterium tuberculosis*-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression  
20 and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent  
25 and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; *see also, Skeiky et al., Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the  
30 purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous



immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine

amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been  
5 exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see *Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at  
10 residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention,  
15 when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of CD4<sup>+</sup> T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further  
20 described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a  
25 growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of  
30 the invention are isolated. An "isolated" polypeptide is one that is removed from its

original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

### Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably an immunogenic variant or derivative, of such a sequence.

5 Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655,  
10 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722,  
15 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-  
25 335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a  
30 polynucleotide sequence of this invention using the methods described herein, (*e.g.*,

BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term "variants" should also be understood to encompass homologous genes of xenogenic origin.

In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to, or complementary to, one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for

20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable  
5 highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides  
10 that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

15 The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment  
20 of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated  
25 to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison  
30 window to identify and compare local regions of sequence similarity. A "comparison

window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

- 5           Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.
- 10 In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson,
- 15 E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

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20 conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics

25 Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402

30 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST

2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always  $>0$ ) and N (penalty score for mismatching residues; always  $<0$ ). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides



that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25

nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 contiguous nucleotides that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of

complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of  
5 contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in  
10 various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger  
15 contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in  
20 length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

25 Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various

factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, e.g., one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to

destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention, polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA<sub>A</sub> receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary,

and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure,  $T_m$ ,  
5 binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary  
10 to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997 Sep 1;25(17):3389-402).

The use of an antisense delivery method employing a short peptide  
15 vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered  
20 into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme  
25 molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For  
30 example, a large number of ribozymes accelerate phosphoester transfer reactions with a

high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement  
5 that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general,  
10 enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to  
15 cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many  
20 technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of  
25 target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action  
30 (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the



specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis  $\delta$  virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis  $\delta$  virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada *et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO

92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells. Ribozymes

expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, *Antisense Nucleic Acid Drug Dev.* 1997 7(4) 431-37). PNA is able to be utilized in a number of methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, *Science*. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, *Bioorg Med Chem.* 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*,

Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will  
5 depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed  
10 by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that  
15 contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and  
20 utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*,  
25 Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in  
30 diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

#### Polynucleotide Identification, Characterization and Expression

Polynucleotide compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by

reference in its entirety. Briefly, in PCR<sup>TM</sup>, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR<sup>TM</sup> amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR<sup>TM</sup> amplification technique, are readily known and available in the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with  $^{32}\text{P}$ ) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then be assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (see Triglia et al., *Nucl. Acids Res.* 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of

amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al.; *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al.; *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.



Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science* 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be

confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

5 In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, i.e., a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing  
10 sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et  
15 al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid,  
20 or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems.

25 The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription  
30 and translation elements, including constitutive and inducible promoters, may be used.

For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSFORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of  $\beta$ -galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For

example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci.* 91:3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which

successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or apt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of

skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

5           A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal  
10 antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul, Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med.* 158:1211-1216).

15           A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions  
20 thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used  
25 include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

          Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained  
30 intracellularly depending on the sequence and/or the vector used. As will be understood

by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.



Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunologically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant ( $K_d$ ) of the interaction, wherein a smaller  $K_d$  represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" ( $K_{on}$ ) and the "off rate constant" ( $K_{off}$ ) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of  $K_{off}/K_{on}$  enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant  $K_d$ . See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as

"framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation

of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "F(ab')<sub>2</sub>" fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V<sub>H</sub>::V<sub>L</sub> heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked V<sub>H</sub>::V<sub>L</sub> heterodimer which is expressed from a gene fusion including V<sub>H</sub>- and V<sub>L</sub>-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated—but chemically separated—light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an

antigen-binding site. See, e.g., U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRs and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (e.g., a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) *Nature* 349:293-299; Lobuglio et al. (1989) *Proc. Nat. Acad. Sci. USA* 86:4220-4224; Shaw et al. (1987) *J Immunol.* 138:4534-4538; and Brown et al. (1987) *Cancer Res.* 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) *Nature* 332:323-327; Verhoeven et al. (1988) *Science* 239:1534-1536; and Jones et al. (1986) *Nature* 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, e.g., a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) *Ann. Rev. Biochem.* 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (e.g., solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (e.g., electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in

this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include  $^{90}\text{Y}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{211}\text{At}$ , and  $^{212}\text{Bi}$ . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the



intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by  
5 serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody.  
10 Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent  
15 bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for  
20 radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For  
25 example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

### T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells

may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et

al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

#### Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as

described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and therapeutic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, e.g., vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve

the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (e.g., U.S. Pat. No. 5,219,740; Miller and Rosman (1989) *BioTechniques* 7:980-990; Miller, A. D. (1990) *Human Gene Therapy* 1:5-14; Scarpa et al. (1991) *Virology* 180:849-852; Burns et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:8033-8037; and Boris-Lawrie and Temin (1993) *Cur. Opin. Genet. Develop.* 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) *J. Virol.* 57:267-274; Bett et al. (1993) *J. Virol.* 67:5911-5921; Mittereder et al. (1994) *Human Gene Therapy* 5:717-729; Seth et al. (1994) *J. Virol.* 68:933-940; Barr et al. (1994) *Gene Therapy* 1:51-58; Berkner, K. L. (1988) *BioTechniques* 6:616-629; and Rich et al. (1993) *Human Gene Therapy* 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, e.g., U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) *Molec. Cell. Biol.* 8:3988-3996; Vincent et al. (1990) *Vaccines 90* (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) *Current Opinion in Biotechnology* 3:533-539; Muzyczka, N. (1992) *Current Topics in Microbiol. and Immunol.* 158:97-129;

Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK<sup>sup</sup>(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, e.g., Elroy-Stein and Moss, Proc. Natl. Acad. Sci. USA (1990) 87:6743-6747; Fuerst et al. Proc. Natl. Acad. Sci. USA (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer

protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, e.g., WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et al. *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in a specific location and orientation via homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the polynucleotide may be stably maintained in the cell as a separate, episomal segment of

DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression  
5 construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable  
10 beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK)  
15 and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device,  
20 propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639  
25 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances  
30 or potentiates an immune response (antibody and/or cell-mediated) to an exogenous



antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins.

5 Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated  
10 sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition  
15 is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN- $\gamma$ , TNF $\alpha$ , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as  
20 provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman,  
25 *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL<sup>®</sup> adjuvants are available from Corixa Corporation (Seattle, WA; see, for example, US  
30 Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing

oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by

5 Sato et al., *Science* 273:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins. Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example

10 combinations of at least two of the following group comprising QS21, QS7, Quil A,  $\beta$ -escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix,

15 particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or

20 suspension, or in a particulate structure such as a paucilamellar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol<sup>R</sup> to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the

25 combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL<sup>®</sup> adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-

MPL<sup>®</sup> adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (e.g., SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn<sup>®</sup>; Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula



wherein,  $n$  is 1-50,  $A$  is a bond or  $-\text{C}(\text{O})-$ ,  $R$  is  $\text{C}_{1-50}$  alkyl or Phenyl  $\text{C}_{1-50}$  alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein  $n$  is between 1 and 50, preferably 4-24, most preferably 9; the  $R$  component is  $\text{C}_{1-50}$ , preferably  $\text{C}_4\text{-C}_{20}$  alkyl and most preferably  $\text{C}_{12}$  alkyl, and  $A$  is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Poxoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck index (12<sup>th</sup> edition: entry 7717). These adjuvant molecules are described in WO

99/52549. The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

5           According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or  
10 maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

15           Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In  
20 general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex*  
25 *vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med.* 4:594-600, 1998).

          Dendritic cells and progenitors may be obtained from peripheral blood,  
30 bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph

nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNF $\alpha$  to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF $\alpha$ , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc $\gamma$  receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or

RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release. In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.*, polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763;

5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems, such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including e.g., oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they

may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.



For oral administration, the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or

by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

- 5 Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered  
10 isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml  
15 of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity  
20 standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for  
25 example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be

administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption  
5 delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase  
10 "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the  
15 lungs *via* nasal aerosol sprays has been described, *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of  
20 a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid  
25 particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example,  
30 Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998

Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

5           Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery  
10 systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, the use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

15           In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)).

          Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the  
20 present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1  $\mu\text{m}$ ) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for  
25 example, by Couvreur *et al.*, Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

Cancer Therapeutic Methods

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of prostate cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., *Immunological Reviews* 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous,

intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

#### Cancer Detection and Diagnostic Compositions, Methods and Kits

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies)

obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the  
5 biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in  
10 the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c)  
15 comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding  
20 agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized  
25 binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and polypeptide portions thereof to which the binding agent binds, as  
30 described above.



The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10  $\mu$ g, and preferably about 100 ng to about 1  $\mu$ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed

and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1  $\mu$ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10

nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the  
5 diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see, for example, Mullis et al., Cold*  
10 *Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules.  
15 PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold  
20 or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above  
25 for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the

cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound  
5 binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific  
10 for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

15 The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein.  
20 Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

25 Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be

present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

5

## EXAMPLES

### EXAMPLE 1

#### ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES

10

This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A<sup>+</sup> RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following  
15 the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A<sup>+</sup> RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen,  
20 Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/NotI site of  
25 pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the  
30 percentage of clones that carried insert, the average insert size and by sequence analysis.



The prostate tumor library contained  $1.64 \times 10^7$  independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained  $3.3 \times 10^6$  independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, 84:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70  $\mu$ g) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100  $\mu$ l of H<sub>2</sub>O, heat-denatured and mixed with 100  $\mu$ l (100  $\mu$ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50  $\mu$ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23  $\mu$ l H<sub>2</sub>O to form the driver DNA.

To form the tracer DNA, 10  $\mu$ g prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5  $\mu$ l H<sub>2</sub>O. Tracer DNA was mixed with 15  $\mu$ l driver DNA and 20  $\mu$ l of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12  $\mu$ l H<sub>2</sub>O, mixed with 8  $\mu$ l driver DNA and 20  $\mu$ l of 2 x hybridization buffer, and subjected to a hybridization at 68

$^{60}\text{C}$  for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK<sup>+</sup> (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted  
5 cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems  
10 Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided  
15 in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA),  
20 human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence  
25 for F1-12 (also referred to as P504S). This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108. cDNA splice variants of P504S are provided in SEQ ID NO: 600-605.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described  
30 above with the normal pancreas cDNA library and with the three most abundant genes

in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to *R. norvegicus* mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S. A cDNA splice variant of P501S is provided in SEQ ID NO: 606.

- 5 In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively.
- 10 Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

- A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences
- 15 with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

- Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and
- 25 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the
- 30

isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the

determination of extended cDNA sequences for 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction  
5 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested,  
10 reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other  
15 normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously  
20 identified ESTs.

Additional studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339. Two variant full-length cDNA sequences for P510S are provided in SEQ ID NO: 535 and 536, with the  
25 corresponding predicted amino acid sequences being provided in SEQ ID NO: 537 and 538, respectively. Additional splice variants of P510S are provided in SEQ ID NO: 598 and 599.

## EXAMPLE 2

## DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE-SPECIFIC POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate-specific polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu$ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin,

small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancreas, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be



over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis *et al.* (*Proc. Natl. Acad. Sci. USA* 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. Subsequent comparison of the sequence of SEQ ID NO: 384 with sequences in the public databases, led to the identification of a full-length cDNA sequence of P1000C (SEQ ID NO: 786), which encodes a 492 amino acid sequence. Analysis of the amino acid sequence using the PSORT II program led to the

identification of a putative transmembrane domain from amino acids 84-100. The cDNA sequence of the open reading frame of P1000C, including the stop codon, is provided in SEQ ID NO: 787, with the open reading frame without the stop codon being provided in SEQ ID NO: 788. The full-length amino acid sequence of P1000C is provided in SEQ ID NO: 789. SEQ ID NO: 790 and 791 represent amino acids 1-100 and 100-492 of P1000C, respectively.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

## EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC  
POLYPEPTIDES BY PCR-BASED SUBTRACTION

5 A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The  
10 resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA  
15 sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID  
20 NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies employing the sequence of SEQ ID NO: 67 as a probe in standard full-length cloning methods, resulted in the isolation of three cDNA sequences  
25 which appear to be splice variants of P80 (also known as P704P). These sequences are provided in SEQ ID NO: 620-622.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA  
30 sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145,

147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones  
5 containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is  
10 provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine  
15 and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed  
20 comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor  
25 compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal  
30 prostate and prostate tumor, compared to six of twelve other normal tissues tested.

Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those  
5 in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

10 PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in  
15 SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX\_23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of  
20 the putative signal sequence. The full-length cDNA sequence for P703P is provided in SEQ ID NO: 524, with the corresponding amino acid sequence being provided in SEQ ID NO: 525.

Using computer algorithms, the following regions of P703P were predicted to represent potential HLA A2-binding CTL epitopes: amino acids 164-172  
25 of SEQ ID NO: 525 (SEQ ID NO: 723); amino acids 160-168 of SEQ ID NO: 525 (SEQ ID NO: 724); amino acids 239-247 of SEQ ID NO: 525 (SEQ ID NO: 725); amino acids 118-126 of SEQ ID NO: 525 (SEQ ID NO: 726); amino acids 112-120 of SEQ ID NO: 525 (SEQ ID NO: 727); amino acids 155-164 of SEQ ID NO: 525 (SEQ ID NO: 728); amino acids 117-126 of SEQ ID NO: 525 (SEQ ID NO: 729); amino acids  
30 164-173 of SEQ ID NO: 525 (SEQ ID NO: 730); amino acids 154-163 of SEQ ID NO:

525 (SEQ ID NO: 731); amino acids 163-172 of SEQ ID NO: 525 (SEQ ID NO: 732); amino acids 58-66 of SEQ ID NO: 525 (SEQ ID NO: 733); and amino acids 59-67 of SEQ ID NO: 525 (SEQ ID NO: 734).

P703P was found to show some homology to previously identified proteases, such as thrombin. The thrombin receptor has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of thrombin receptor antisense cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against thrombin receptor inhibit thrombin receptor activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P may play a role in prostate cancer through a protease-activated receptor on the cancer cell or on stromal cells. The potential trypsin-like protease activity of P703P may either activate a protease-activated receptor on the cancer cell membrane to promote tumorigenesis or activate a protease-activated receptor on the adjacent cells (such as stromal cells) to secrete growth factors and/or proteases (such as matrix metalloproteinases) that could promote tumor angiogenesis, invasion and metastasis. P703P may thus promote tumor progression and/or metastasis through the activation of protease-activated receptor. Polypeptides and antibodies that block the P703P-receptor interaction may therefore be usefully employed in the treatment of prostate cancer.

To determine whether P703P expression increases with increased severity of Gleason grade, an indicator of tumor stage, quantitative PCR analysis was performed on prostate tumor samples with a range of Gleason scores from 5 to > 8. The mean level of P703P expression increased with increasing Gleason score, indicating that P703P expression may correlate with increased disease severity.

Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are

provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

Further studies led to the isolation of an extended cDNA sequence for P712P (SEQ ID NO: 552). The amino acid sequences encoded by 16 predicted open reading frames present within the sequence of SEQ ID NO: 552 are provided in SEQ ID NO: 553-568.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P



were found. Further studies employing the sequence of SEQ ID NO: 334 as a probe in standard full-length cloning methods, resulted in an extended cDNA sequence for P714P. This sequence is provided in SEQ ID NO: 619. This sequence was found to show some homology to the gene that encodes human ribosomal L23A protein.

5 Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

10 Further studies on P775P resulted in the isolation of four additional sequences (SEQ ID NO: 473-476) which are all splice variants of the P775P gene. The sequence of SEQ ID NO: 474 was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 477 and 478. The cDNA sequence of SEQ ID NO: 475 was found to contain an  
15 ORF which encodes the amino acid sequence of SEQ ID NO: 479. The cDNA sequence of SEQ ID NO: 473 was found to contain four ORFs. The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 480-483. Additional splice variants of P775P are provided in SEQ ID NO: 593-597.

Subsequent studies led to the identification of a genomic region on  
20 chromosome 22q11.2, known as the Cat Eye Syndrome region, that contains the five prostate genes P704P, P712P, P774P, P775P and B305D. The relative location of each of these five genes within the genomic region is shown in Fig. 10. This region may therefore be associated with malignant tumors, and other potential tumor genes may be contained within this region. These studies also led to the identification of a potential  
25 open reading frame (ORF) for P775P (provided in SEQ ID NO: 533), which encodes the amino acid sequence of SEQ ID NO: 534.

Comparison of the clone of SEQ ID NO: 325 (referred to as P558S) with sequences in the GenBank and GeneSeq DNA databases showed that P558S is identical to the prostate-specific transglutaminase gene, which is known to have two forms. The  
30 full-length sequences for the two forms are provided in SEQ ID NO: 630 and 631, with

the corresponding amino acid sequences being provided in SEQ ID NO: 632 and 633, respectively. The cDNA sequence of SEQ ID NO: 631 has a 15 pair base insert, resulting in a 5 amino acid insert in the corresponding amino acid sequence (SEQ ID NO: 633). This insert is not present in the sequence of SEQ ID NO: 630.

5 Further studies on P768P (SEQ ID NO: 315) led to the identification of the putative full-length open reading frame (ORF). The cDNA sequence of the ORF with stop codon is provided in SEQ ID NO: 764. The cDNA sequence of the ORF without stop codon is provided in SEQ ID NO: 765, with the corresponding amino acid sequence being provided in SEQ ID NO: 766. This sequence was found to show 86%  
10 identity to a rat calcium transporter protein, indicating that P768P may represent a human calcium transporter protein. The locations of transmembrane domains within P768P were predicted using the PSORT II computer algorithm. Six transmembrane domains were predicted at amino acid positions 118-134, 172-188, 211-227, 230-246, 282-298 and 348-364. The amino acid sequences of SEQ ID NO: 767-772 represent  
15 amino acids 1-134, 135-188, 189-227, 228-246, 247-298 and 299-511 of P768P, respectively.

#### EXAMPLE 4

##### SYNTHESIS OF POLYPEPTIDES

20

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of  
25 conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid  
30 (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of

0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

5

### EXAMPLE 5

#### FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

10 A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide  
15 restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

20

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate  
25 hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences  
30 which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich  
5 differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

10 In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for  
15 proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA  
20 sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant  
25 homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most  
30 prostate tumors and BPH tissues by a factor of three or greater, with elevated expression

seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

5 Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349,  
10 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 11 (SEQ ID NO: 340-349 and 362) were found to show some homology to previously identified sequences. No significant  
15 homologies were found to the clones of SEQ ID NO: 350, 351, 353-361, and 363-365.

Comparison of the sequence of SEQ ID NO: 362 with sequences in the GenBank and GeneSeq DNA databases showed that this clone (referred to as P788P) is identical to GeneSeq Accession No. X27262, which encodes a protein found in the GeneSeq protein Accession No. Y00931. The full length cDNA sequence of P788P is  
20 provided in SEQ ID NO: 634, with the corresponding predicted amino acid being provided in SEQ ID NO: 635. Subsequently, a full-length cDNA sequence for P788P that contains polymorphisms not found in the sequence of SEQ ID NO: 634, was cloned multiple times by PCR amplification from cDNA prepared from several RNA templates from three individuals. This determined cDNA sequence of this polymorphic variant of  
25 P788P is provided in SEQ ID NO: 636, with the corresponding amino acid sequence being provided in SEQ ID NO: 637. The sequence of SEQ ID NO: 637 differs from that of SEQ ID NO: 635 by six amino acid residues. The P788P protein has 7 potential transmembrane domains at the C-terminal portion and is predicted to be a plasma membrane protein with an extracellular N-terminal region.

Further studies on the clone of SEQ ID NO: 352 (referred to as P790P) led to the isolation of the full-length cDNA sequence of SEQ ID NO: 526. The corresponding predicted amino acid is provided in SEQ ID NO: 527. Data from two quantitative PCR experiments indicated that P790P is over-expressed in 11/15 tested prostate tumor samples and is expressed at low levels in spinal cord, with no expression being seen in all other normal samples tested. Data from further PCR experiments and microarray experiments showed over-expression in normal prostate and prostate tumor with little or no expression in other tissues tested. P790P was subsequently found to show significant homology to a previously identified G-protein coupled prostate tissue receptor.

Additional studies on the clone of SEQ ID NO: 354 (referred to as P776P) led to the isolation of an extended cDNA sequence, provided in SEQ ID NO: 569. The determined cDNA sequences of three additional splice variants of P776P are provided in SEQ ID NO: 570-572. The amino acid sequences encoded by two predicted open reading frames (ORFs) contained within SEQ ID NO: 570, one predicted ORF contained within SEQ ID NO: 571, and 11 predicted ORFs contained within SEQ ID NO: 569, are provided in SEQ ID NO: 573-586, respectively. Further studies led to the isolation of the full-length sequence for the clone of SEQ ID NO: 570 (provided in SEQ ID NO: 737). Full-length cloning efforts on the clone of SEQ ID NO: 571 led to the isolation of two sequences (provided in SEQ ID NO: 738 and 739), representing a single clone, that are identical with the exception of a polymorphic insertion/deletion at position 1293. Specifically, the clone of SEQ ID NO: 739 (referred to as clone F1) has a C at position 1293. The clone of SEQ ID NO: 738 (referred to as clone F2) has a single base pair deletion at position 1293. The predicted amino acid sequences encoded by 5 open reading frames located within SEQ ID NO: 737 are provided in SEQ ID NO: 740-744, with the predicted amino acid sequences encoded by the clone of SEQ ID NO: 738 and 739 being provided in SEQ ID NO: 745-750.

Comparison of the cDNA sequences for the clones P767P (SEQ ID NO: 314) and P777P (SEQ ID NO: 350) with sequences in the GenBank human EST database showed that the two clones matched many EST sequences in common,

suggesting that P767P and P777P may represent the same gene. A DNA consensus sequence derived from a DNA sequence alignment of P767P, P777P and multiple EST clones is provided in SEQ ID NO: 587. The amino acid sequences encoded by three putative ORFs located within SEQ ID NO: 587 are provided in SEQ ID NO: 588-590.

5 The clone of SEQ ID NO: 342 (referred to as P789P) was found to show homology to a previously identified gene. The full length cDNA sequence for P789P and the corresponding amino acid sequence are provided in SEQ ID NO: 735 and 736, respectively.

#### 10 EXAMPLE 6

##### PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

15 Mice expressing the transgene for human HLA A2Kb (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., *Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995 with the following modifications. Mice were  
20 immunized with 100µg of P2S#12 and 120µg of an I-A<sup>b</sup> binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at  $6 \times 10^6$  cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium  
25 pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL),  $2 \times 10^{-5}$  M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells ( $5 \times 10^5$ /ml) were  
30 restimulated with  $2.5 \times 10^6$ /ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells

(Sherman et al, *Science* 258:815-818, 1992) and  $3 \times 10^6$ /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells ( $1 \times 10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders ( $5 \times 10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2Kb expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2Kb molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, *J. Immunol.*, 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200  $\mu$ g/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes,



CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

5 Mice expressing the transgene for human HLA A2Kb were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5µg of P1S #10 and 120µg of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single  
10 cell suspensions prepared using a nylon mesh. Cells were then resuspended at  $6 \times 10^6$  cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2µg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later cells ( $5 \times 10^5$ /ml) were restimulated  
15 with  $2.5 \times 10^6$ /ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and  $3 \times 10^6$ /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as  
20 shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells ( $1 \times 10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders ( $5 \times 10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were  
25 isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

## EXAMPLE 7

PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION  
WITH A PROSTATE ANTIGEN

The prostate-specific antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 µg P501S in the vector VR1012 either intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL responses. These results demonstrate that P501S contains at least one naturally processed HLA-A2-restricted CTL epitope.

## EXAMPLE 8

## ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE-SPECIFIC POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human CD8<sup>+</sup> T cells were primed *in vitro* to the P2S-12 peptide (SEQ ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to the protocol of Van Tsai et al. (*Critical Reviews in Immunology* 18:65-75, 1998). The resulting CD8<sup>+</sup> T cell microcultures were tested for their ability to recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a  $\gamma$ -interferon ELISPOT assay (see Lalvani et al., *J. Exp. Med.* 186:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on 10<sup>4</sup> fibroblasts in the presence of 3 µg/ml human  $\beta_2$ -microglobulin and 1 µg/ml P2S-12 peptide or control E75 peptide. In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with HER-2/*neu*. Prior to the assay, the

fibroblasts were treated with 10 ng/ml  $\gamma$ -interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a  $\gamma$ -interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of  $\gamma$ -interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of  $\gamma$ -interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/*neu* gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

## EXAMPLE 9

### ELICITATION OF PROSTATE ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate-specific antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GM-CSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8<sup>+</sup> cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles using autologous fibroblasts

retrovirally transduced to express P501S and CD80, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxicity assays ( $^{51}\text{Cr}$  release) and interferon-gamma production (Interferon-gamma Elispot; *see* above and Lalvani et al., *J. Exp. Med.* 186:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

10

## EXAMPLE 10

IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN THE  
PROSTATE-SPECIFIC ANTIGEN P703P

15

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific human CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed and P703P-transduced target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2Kb transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of HLA-A2Kb or HLA-A2 transduced target cells expressing P703P.

Initial studies demonstrating that p5 is a naturally processed epitope were done using HLA-A2Kb transgenic mice. HLA-A2Kb transgenic mice were immunized subcutaneously in the footpad with 100  $\mu\text{g}$  of p5 peptide together with 140  $\mu\text{g}$  of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the

30

control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in  
5 RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with 1 ug/ml p5 peptide and cultured with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures,  
10 CTL recognition of p5-pulsed target cells was demonstrated. CTL were additionally shown to recognize human cells transduced to express P703P, demonstrating that p5 is a naturally processed epitope.

Studies identifying a further peptide epitope (referred to as peptide 4) derived from the prostate tumor-specific antigen P703P that is capable of being  
15 recognized by CD4 T cells on the surface of cells in the context of HLA class II molecules were carried out as follows. The amino acid sequence for peptide 4 is provided in SEQ ID NO: 638, with the corresponding cDNA sequence being provided in SEQ ID NO: 639.

Twenty 15-mer peptides overlapping by 10 amino acids and derived  
20 from the carboxy-terminal fragment of P703P were generated using standard procedures. Dendritic cells (DC) were derived from PBMC of a normal female donor using GM-CSF and IL-4 by standard protocols. CD4 T cells were generated from the same donor as the DC using MACS beads and negative selection. DC were pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration  
25 of 0.25 microgram/ml. Pulsed DC were washed and plated at  $1 \times 10^4$  cells/well of 96-well V-bottom plates and purified CD4 T cells were added at  $1 \times 10^5$ /well. Cultures were supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37 °C. Cultures were restimulated as above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 u/ml IL-2.  
30 Following 4 *in vitro* stimulation cycles, 96 lines (each line corresponding to one well) were tested for specific proliferation and cytokine production in response to the

stimulating pools with an irrelevant pool of peptides derived from mammaglobin being used as a control.

One line (referred to as 1-F9) was identified from pool #1 that demonstrated specific proliferation (measured by <sup>3</sup>H proliferation assays) and cytokine production (measured by interferon-gamma ELISA assays) in response to pool #1 of P703P peptides. This line was further tested for specific recognition of the peptide pool, specific recognition of individual peptides in the pool, and in HLA mismatch analyses to identify the relevant restricting allele. Line 1-F9 was found to specifically proliferate and produce interferon-gamma in response to peptide pool #1, and also to peptide 4 (SEQ ID NO: 638). Peptide 4 corresponds to amino acids 126-140 of SEQ ID NO: 327. Peptide titration experiments were conducted to assess the sensitivity of line 1-F9 for the specific peptide. The line was found to specifically respond to peptide 4 at concentrations as low as 0.25 ng/ml, indicating that the T cells are very sensitive and therefore likely to have high affinity for the epitope.

To determine the HLA restriction of the P703P response, a panel of antigen presenting cells (APC) was generated that was partially matched with the donor used to generate the T cells. The APC were pulsed with the peptide and used in proliferation and cytokine assays together with line 1-F9. APC matched with the donor at HLA-DRB0701 and HLA-DQB02 alleles were able to present the peptide to the T cells, indicating that the P703P-specific response is restricted to one of these alleles.

Antibody blocking assays were utilized to determine if the restricting allele was HLA-DR0701 or HLA-DQ02. The anti-HLA-DR blocking antibody L243 or an irrelevant isotype matched IgG2a were added to T cells and APC cultures pulsed with the peptide RMPTVLQCVNVS VVS (SEQ ID NO: 638) at 250 ng/ml. Standard interferon-gamma and proliferation assays were performed. Whereas the control antibody had no effect on the ability of the T cells to recognize peptide-pulsed APC, in both assays the anti-HLA-DR antibody completely blocked the ability of the T cells to specifically recognize peptide-pulsed APC.

To determine if the peptide epitope RMPTVLQCVNVS VVS (SEQ ID NO: 638) was naturally processed, the ability of line 1-F9 to recognize APC pulsed with recombinant P703P protein was examined. For these experiments a number of

recombinant P703P sources were utilized; *E. coli*-derived P703P, Pichia-derived P703P and baculovirus-derived P703P. Irrelevant protein controls used were *E. coli*-derived L3E (a lung-specific antigen) and baculovirus-derived mammaglobin. In interferon-gamma ELISA assays, line 1-F9 was able to efficiently recognize both *E. coli* forms of P703P as well as Pichia-derived recombinant P703P, while baculovirus-derived P703P was recognized less efficiently. Subsequent Western blot analysis revealed that the *E. coli* and Pichia P703P protein preparations were intact while the baculovirus P703P preparation was approximately 75% degraded. Thus, peptide RMPTVLQCVNVS VVS (SEQ ID NO: 638) from P703P is a naturally processed peptide epitope derived from P703P and presented to T cells in the context of HLA-DRB-0701

In further studies, twenty-four 15-mer peptides overlapping by 10 amino acids and derived from the N-terminal fragment of P703P (corresponding to amino acids 27-154 of SEQ ID NO: 525) were generated by standard procedures and their ability to be recognized by CD4 cells was determined essentially as described above. DC were pulsed overnight with pools of the peptides with each peptide at a final concentration of 10 microgram/ml. A large number of individual CD4 T cell lines (65/480) demonstrated significant proliferation and cytokine release (IFN-gamma) in response to the P703P peptide pools but not to a control peptide pool. The CD4 T cell lines which demonstrated specific activity were restimulated on the appropriate pool of P703P peptides and reassayed on the individual peptides of each pool as well as a peptide dose titration of the pool of peptides in a IFN-gamma release assay and in a proliferation assay.

Sixteen immunogenic peptides were recognized by the T cells from the entire set of peptide antigens tested. The amino acid sequences of these peptides are provided in SEQ ID NO: 656-671, with the corresponding cDNA sequences being provided in SEQ ID NO: 640-655, respectively. In some cases the peptide reactivity of the T cell line could be mapped to a single peptide, however some could be mapped to more than one peptide in each pool. Those CD4 T cell lines that displayed a representative pattern of recognition from each peptide pool with a reasonable affinity for peptide were chosen for further analysis (I-1A, -6A; II-4C, -5E; III-6E, IV-4B, -3F, -9B, -10F, V-5B, -4D, and -10F). These CD4 T cell lines were restimulated on the

appropriate individual peptide and reassayed on autologous DC pulsed with a truncated form of recombinant P703P protein made in *E. coli* (a.a. 96 - 254 of SEQ ID NO: 525), full-length P703P made in the baculovirus expression system, and a fusion between influenza virus NS1 and P703P made in *E. coli*. Of the T cell lines tested; line I-1A  
5 recognized specifically the truncated form of P703P (*E. coli*) but no other recombinant form of P703P. This line also recognized the peptide used to elicit the T cells. Line 2-4C recognized the truncated form of P703P (*E. coli*) and the full length form of P703P made in baculovirus, as well as peptide. The remaining T cell lines tested were either peptide-specific only (II-5E, II-6F, IV-4B, IV-3F, IV-9B, IV-10F, V-5B and V-4D) or  
10 were non-responsive to any antigen tested (V-10F). These results demonstrate that the peptide sequence RPLLANDLMLIKLDE (SEQ ID NO: 671; corresponding to a.a. 110-124 of SEQ ID NO: 525) recognized by the T cell line I-1A, and the peptide sequences SVSESDTIRSISIAS (SEQ ID NO: 668; corresponding to a.a. 125-139 of SEQ ID NO: 525) and ISIASQCPTAGNSCL (SEQ ID NO: 667; corresponding to a.a. 135-149 of  
15 SEQ ID NO: 525) recognized by the T cell line II-4C may be naturally processed epitopes of the P703P protein.

### EXAMPLE 11

#### EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

20 Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences  
25 for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively. In further studies, a splice variant of the cDNA sequence of SEQ ID NO: 366 was isolated which was found to contain an additional guanine residue at position 884 (SEQ ID NO: 530), leading to a  
30 frameshift in the open reading frame. The determined DNA sequence of this ORF is



provided in SEQ ID NO: 531. This frameshift generates a protein sequence (provided in SEQ ID NO: 532) of 293 amino acids that contains the C-terminal domain common to the other isoforms of B305D but that differs in the N-terminal region.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach). Using real-time PCR on a panel of prostate tumors, expression of B305D in prostate tumors was shown to increase with increasing Gleason grade, demonstrating that expression of B305D increases as prostate cancer progresses.

#### EXAMPLE 12

##### 15 GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH THE PROSTATE-SPECIFIC ANTIGEN P501S

Using *in vitro* whole-gene priming with P501S-vaccinia infected DC (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon- $\gamma$  ELISPOT analysis as described above. Using a panel of HLA-mismatched B-LCL lines transduced with P501S, these CTL lines were shown to be likely restricted to HLAB class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3  $\mu$ g/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated

using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S and CD80. Following four stimulation cycles, CD8<sup>+</sup> T cell lines were identified that specifically produced interferon- $\gamma$  when stimulated with P501S and CD80-transduced autologous  
5 fibroblasts. A panel of HLA-mismatched B-LCL lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon- $\gamma$  in an ELISPOT assay, the P501S specific response was shown to be likely restricted by HLA B alleles. These results demonstrate that a CD8<sup>+</sup> CTL response to P501S can be elicited.

10 To identify the epitope(s) recognized, cDNA encoding P501S was fragmented by various restriction digests, and sub-cloned into the retroviral expression vector pBIB-KS. Retroviral supernatants were generated by transfection of the helper packaging line Phoenix-Ampho. Supernatants were then used to transduce Jurkat/A2Kb cells for CTL screening. CTL were screened in IFN-gamma ELISPOT  
15 assays against these A2Kb targets transduced with the "library" of P501S fragments. Initial positive fragments P501S/H3 and P501S/F2 were sequenced and found to encode amino acids 106-553 and amino acids 136-547, respectively, of SEQ ID NO: 113. A truncation of H3 was made to encode amino acid residues 106-351 of SEQ ID NO: 113, which was unable to stimulate the CTL, thus localizing the epitope to amino acid  
20 residues 351-547. Additional fragments encoding amino acids 1-472 (Fragment A) and amino acids 1-351 (Fragment B) were also constructed. Fragment A but not Fragment B stimulated the CTL thus localizing the epitope to amino acid residues 351-472. Overlapping 20-mer and 18-mer peptides representing this region were tested by pulsing Jurkat/A2Kb cells versus CTL in an IFN-gamma assay. Only peptides P501S-369(20)  
25 and P501S-369(18) stimulated the CTL. Nine-mer and 10-mer peptides representing this region were synthesized and similarly tested. Peptide P501S-370 (SEQ ID NO: 539) was the minimal 9-mer giving a strong response. Peptide P501S-376 (SEQ ID NO: 540) also gave a weak response, suggesting that it might represent a cross-reactive epitope.

In subsequent studies, the ability of primary human B cells transduced with P501S to prime MHC class I-restricted, P501S-specific, autologous CD8 T cells was examined. Primary B cells were derived from PBMC of a homozygous HLA-A2 donor by culture in CD40 ligand and IL-4, transduced at high frequency with recombinant P501S in the vector pBIB, and selected with blastocidin-S. For *in vitro* priming, purified CD8+ T cells were cultured with autologous CD40 ligand + IL-4 derived, P501S-transduced B cells in a 96-well microculture format. These CTL microcultures were re-stimulated with P501S-transduced B cells and then assayed for specificity. Following this initial screen, microcultures with significant signal above background were cloned on autologous EBV-transformed B cells (BLCL), also transduced with P501S. Using IFN-gamma ELISPOT for detection, several of these CD8 T cell clones were found to be specific for P501S, as demonstrated by reactivity to BLCL/P501S but not BLCL transduced with control antigen. It was further demonstrated that the anti-P501S CD8 T cell specificity is HLA-A2-restricted. First, antibody blocking experiments with anti-HLA-A,B,C monoclonal antibody (W6.32), anti-HLA-B,C monoclonal antibody (B1.23.2) and a control monoclonal antibody showed that only the anti-HLA-A,B,C antibody blocked recognition of P501S-expressing autologous BLCL. Secondly, the anti-P501S CTL also recognized an HLA-A2 matched, heterologous BLCL transduced with P501S, but not the corresponding EGFP transduced control BLCL.

A naturally processed, CD8, class I-restricted peptide epitope of P501S was identified as follows. Dendritic Cells (DC) were isolated by Percol gradient followed by differential adherence, and cultured for 5 days in the presence of RPMI medium containing 1% human serum, 50ng/ml GM-CSF and 30ng/ml IL-4. Following culture, DC were infected for 24 hours with P501S-expressing adenovirus at an MOI of 10 and matured for an additional 24 hours by the addition of 2ug/ml CD40 ligand. CD8 cells were enriched for by the subtraction of CD4+, CD14+ and CD16+ populations from PBMC with magnetic beads. Priming cultures containing 10,000 P501S-expressing DC and 100,000 CD8+ T cells per well were set up in 96-well V-bottom plates with RPMI containing 10% human serum, 5ng/ml IL-12 and 10ng/ml IL-6. Cultures were stimulated every 7 days using autologous fibroblasts retrovirally

transduced to express P501S and CD80, and were treated with IFN-gamma for 48-72 hours to upregulate MHC Class I expression. 10u/ml IL-2 was added at the time of stimulation and on days 2 and 5 following stimulation. Following 4 stimulation cycles, one P501S-specific CD8+ T cell line (referred to as 2A2) was identified that produced IFN-gamma in response to IFN-gamma-treated P501S/CD80 expressing autologous fibroblasts, but not in response to IFN-gamma-treated P703P/CD80 expressing autologous fibroblasts in a  $\gamma$ -IFN Elispot assay. Line 2A2 was cloned in 96-well plates with 0.5 cell/well or 2 cells/well in the presence of 75,000 PBMC/well, 10,000 B-LCL/well, 30ng/ml OKT3 and 50u/ml IL-2. Twelve clones were isolated that showed strong P501S specificity in response to transduced fibroblasts.

Fluorescence activated cell sorting (FACS) analysis was performed on P501S-specific clones using CD3-, CD4- and CD8-specific antibodies conjugated to PercP, FITC and PE respectively. Consistent with the use of CD8 enriched T cells in the priming cultures, P5401S-specific clones were determined to be CD3+, CD8+ and CD4-.

To identify the relevant P501S epitope recognized by P501S specific CTL, pools of 18-20 mer or 30-mer peptides that spanned the majority of the amino acid sequence of P501S were loaded onto autologous B-LCL and tested in  $\gamma$ -IFN Elispot assays for the ability to stimulate two P501S-specific CTL clones, referred to as 4E5 and 4E7. One pool, composed of five 18-20 mer peptides that spanned amino acids 411-486 of P501S (SEQ ID NO: 113), was found to be recognized by both P501S-specific clones. To identify the specific 18-20 mer peptide recognized by the clones, each of the 18-20 mer peptides that comprised the positive pool were tested individually in  $\gamma$ -IFN Elispot assays for the ability to stimulate the two P501S-specific CTL clones, 4E5 and 4E7. Both 4E5 and 4E7 specifically recognized one 20-mer peptide (SEQ ID NO: 710; cDNA sequence provided in SEQ ID NO: 711) that spanned amino acids 453-472 of P501S. Since the minimal epitope recognized by CD8+ T cells is almost always either a 9 or 10-mer peptide sequence, 10-mer peptides that spanned the entire sequence of SEQ ID NO: 710 were synthesized that differed by 1 amino acid. Each of these 10-mer peptides was tested for the ability to stimulate two P501S-specific clones, (referred to as 1D5 and 1E12). One 10-mer peptide (SEQ ID NO: 712; cDNA sequence provided in

SEQ ID NO: 713) was identified that specifically stimulated the P501S-specific clones. This epitope spans amino acids 463-472 of P501S. This sequence defines a minimal 10-mer epitope from P501S that can be naturally processed and to which CTL responses can be identified in normal PBMC. Thus, this epitope is a candidate for use as a vaccine moiety, and as a therapeutic and/or diagnostic reagent for prostate cancer.

To identify the class I restriction element for the P501S-derived sequence of SEQ ID NO: 712, HLA blocking and mismatch analyses were performed. In  $\gamma$ -IFN Elispot assays, the specific response of clones 4A7 and 4E5 to P501S-transduced autologous fibroblasts was blocked by pre-incubation with 25ug/ml W6/32 (pan-Class I blocking antibody) and B1.23.2 (HLA-B/C blocking antibody). These results demonstrate that the SEQ ID NO: 712-specific response is restricted to an HLA-B or HLA-C allele.

For the HLA mismatch analysis, autologous B-LCL (HLA-A1,A2,B8,B51, Cw1, Cw7) and heterologous B-LCL (HLA-A2,A3,B18,B51,Cw5,Cw14) that share the HLAB51 allele were pulsed for one hour with 20ug/ml of peptide of SEQ ID NO: 712, washed, and tested in  $\gamma$ -IFN Elispot assays for the ability to stimulate clones 4A7 and 4E5. Antibody blocking assays with the B1.23.2 (HLA-B/C blocking antibody) were also performed. SEQ ID NO: 712-specific response was detected using both the autologous (D326) and heterologous (D107) B-LCL, and furthermore the responses were blocked by pre-incubation with 25ug/ml of B1.23.2 HLA-B/C blocking antibody. Together these results demonstrate that the P501S-specific response to the peptide of SEQ ID NO: 712 is restricted to the HLA-B51 class I allele. Molecular cloning and sequence analysis of the HLA-B51 allele from D3326 revealed that the HLA-B51 subtype of D326 is HLA-B51011.

Based on the 10-mer P501S-derived epitope of SEQ ID NO: 712, two 9-mers with the sequences of SEQ ID NO: 714 and 715 were synthesized and tested in Elispot assays for the ability to stimulate two P501S-specific CTL clones derived from line 2A2. The 10-mer peptide of SEQ ID NO: 712, as well as the 9-mer peptide of SEQ ID NO: 715, but not the 9-mer peptide of SEQ ID NO: 714, were capable of stimulating the P501S-specific CTL to produce IFN-gamma. These results demonstrate that the peptide of SEQ ID NO: 715 is a 9-mer P501S-derived epitope recognized by P501S-

specific CTL. The DNA sequence encoding the epitope of SEQ ID NO: 715 is provided in SEQ ID NO: 716.

To identify the class I restricting allele for the P501S-derived peptide of SEQ ID NO: 712 and 715 specific response, each of the HLA B and C alleles were  
5 cloned from the donor used in the *in vitro* priming experiment. Sequence analysis indicated that the relevant alleles were HLA-B8, HLA-B51, HLA-Cw01 and HLA-Cw07. Each of these alleles were subcloned into an expression vector and co-transfected together with the P501S gene into VA-13 cells. Transfected VA-13 cells were then tested for the ability to specifically stimulate the P501S-specific CTL in  
10 ELISPOT assays. VA-13 cells transfected with P501S and HLA-B51 were capable of stimulating the P501S-specific CTL to secrete gamma-IFN. VA-13 cells transfected with HLA-B51 alone or P501S + the other HLA-alleles were not capable of stimulating the P501S-specific CTL. These results demonstrate that the restricting allele for the P501S-specific response is the HLAB51 allele. Sequence analysis revealed that the  
15 subtype of the relevant restricting allele is HLA-B51011.

To determine if the P501S-specific CTL could recognize prostate tumor cells that express P501S, the P501S-positive lines LnCAP and CRL2422 (both expressing "moderate" amounts of P501S mRNA and protein), and PC-3 (expressing low amounts of P501S mRNA and protein), plus the P501S-negative cell line DU-145  
20 were retrovirally transduced with the HLA-B51011 allele that was cloned from the donor used to generate the P501S-specific CTL. HLA-B51011- or EGFP-transduced and selected tumor cells were treated with gamma-interferon and androgen (to upregulate stimulatory functions and P501S, respectively) and used in gamma-interferon Elispot assays with the P501S-specific CTL clones 4E5 and 4E7. Untreated  
25 cells were used as a control.

Both 4E5 and 4E7 efficiently and specifically recognized LnCAP and CRL2422 cells that were transduced with the HLA-B51011 allele, but not the same cell lines transduced with EGFP. Additionally, both CTL clones specifically recognized PC-3 cells transduced with HLA-B51011, but not the P501S-negative tumor cell line  
30 DU-145. Treatment with gamma-interferon or androgen did not enhance the ability of CTL to recognize tumor cells. These results demonstrate that P501S-specific CTL,

generated by *in vitro* whole gene priming, specifically and efficiently recognize prostate tumor cell lines that express P501S.

A naturally processed CD4 epitope of P501S was identified as follows.

CD4 cells specific for P501S were prepared as described above. A series of 16 overlapping peptides were synthesized that spanned approximately 50% of the amino terminal portion of the P501S gene (amino acids 1- 325 of SEQ ID NO: 113). For priming, peptides were combined into pools of 4 peptides, pulsed at 4 µg/ml onto dendritic cells (DC) for 24 hours, with TNF-alpha. DC were then washed and mixed with negatively selected CD4+ T cells in 96 well U-bottom plates. Cultures were re-stimulated weekly on fresh DC loaded with peptide pools. Following a total of 4 stimulation cycles, cells were rested for an additional week and tested for specificity to APC pulsed with peptide pools using γ-IFN ELISA and proliferation assays. For these assays, adherent monocytes loaded with either the relevant peptide pool at 4ug/ml or an irrelevant peptide at µg/ml were used as APC. T cell lines that demonstrated either specific cytokine secretion or proliferation were then tested for recognition of individual peptides that were present in the pool. T cell lines could be identified from pools A and B that recognized individual peptides from these pools.

From pool A, lines AD9 and AE10 specifically recognized peptide 1 (SEQ ID NO: 719), and line AF5 recognized peptide 39 (SEQ ID NO: 718). From pool B, line BC6 could be identified that recognized peptide 58 (SEQ ID NO: 717). Each of these lines were stimulated on the specific peptide and tested for specific recognition of the peptide in a titration assay as well as cell lysates generated by infection of HEK 293 cells with adenovirus expressing either P501S or an irrelevant antigen. For these assays, APC-adherent monocytes were pulsed with either 10, 1, or 0.1  $\mu$ g/ml individual P501S peptides, and DC were pulsed overnight with a 1:5 dilution of adenovirally infected cell lysates. Lines AD9, AE10 and AF5 retained significant recognition of the relevant P501S-derived peptides even at 0.1 mg/ml. Furthermore, line AD9 demonstrated significant (8.1 fold stimulation index) specific activity for lysates from adenovirus-P501S infected cells. These results demonstrate that high affinity CD4 T cell lines can be generated toward P501S-derived epitopes, and that at least a subset of these T cells specific for the P501S derived sequence of SEQ ID NO: 719 are specific for an epitope that is naturally processed by human cells. The DNA sequences encoding the amino acid sequences of SEQ ID NO: 717-719 are provided in SEQ ID NO: 720-722, respectively.

To further characterize the P501S-specific activity of AD9, the line was cloned using anti-CD3. Three clones, referred to as 1A1, 1A9 and 1F5, were identified that were specific for the P501S-1 peptide (SEQ ID NO: 719). To determine the HLA restriction allele for the P501S-specific response, each of these clones was tested in class II antibody blocking and HLA mismatch assays using proliferation and gamma-interferon assays. In antibody blocking assays and measuring gamma-interferon production using ELISA assays, the ability of all three clones to recognize peptide pulsed APC was specifically blocked by co-incubation with either a pan-class II blocking antibody or a HLA-DR blocking antibody, but not with a HLA-DQ or an irrelevant antibody. Proliferation assays performed simultaneously with the same cells confirmed these results. These data indicate that the P501S-specific response of the clones is restricted by an HLA-DR allele. Further studies demonstrated that the restricting allele for the P501S-specific response is HLA-DRB1501.



**EXAMPLE 13****IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS  
BY MICROARRAY ANALYSIS**

5           This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

          A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to  
10 non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-  
15 400) correspond to known sequences, as shown in Table I.

Table I  
Summary of Prostate Tumor Antigens

Known Genes	Previously Identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-Iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang (23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other

normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 (also referred to as P553S) showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

Subsequent full-length cloning studies on P553S, using standard techniques, revealed that this clone is an incomplete spliced form of P501S. The determined cDNA sequences for four splice variants of P553S are provided in SEQ ID NO: 623-626. An amino acid sequence encoded by SEQ ID NO: 626 is provided in SEQ ID NO: 627. The cDNA sequence of SEQ ID NO: 623 was found to contain two open reading frames (ORFs). The amino acid sequences encoded by these two ORFs are provided in SEQ ID NO: 628 and 629.

#### EXAMPLE 14

#### IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate-specific antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA* 95:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups: Plus (normal prostate and prostate tumor libraries, and breast cell line libraries, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (libraries from fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

**Table II**  
**Prostate cDNA Libraries and ESTs**

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

5 Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones derived from the Plus and Other group libraries only; no expression detected in the  
10 Minus group; Type 3- EST clones derived from the Plus, Minus and Other group libraries, but the number of ESTs derived from the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones derived from Plus, Minus and Other group libraries, but the number derived from the Plus group is higher than the number derived from the Minus group. This analysis identified 4,345 breast clusters  
15 (see Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

Table III  
Prostate Cluster Summary

Type	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

5           The EST clone inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high levels  
10 of tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes  
15 generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

          Clones with an expression ratio greater than 3 (*i.e.*, the level in prostate tumor and normal prostate mRNA was at least three times the level in other normal tissue mRNA) were identified as prostate tumor-specific sequences (Table IV). The  
20 sequences of these clones are provided in SEQ ID NO: 401-453, with certain novel sequences shown in SEQ ID NO: 407, 413, 416-419, 422, 426, 427 and 450.

Table IV  
Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57



439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

Further studies on the clone of SEQ ID NO: 407 (also referred to as P1020C) led to the isolation of an extended cDNA sequence provided in SEQ ID NO: 591. This extended cDNA sequence was found to contain an open reading frame that  
5 encodes the predicted amino acid sequence of SEQ ID NO: 592. The P1020C cDNA and amino acid sequences were found to show some similarity to the human endogenous retroviral HERV-K pol gene and protein.

#### EXAMPLE 15

##### 10 FURTHER IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above  
15 was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NO: 454-467. Of these sequences, SEQ ID NO: 459-460 represent novel genes. The others (SEQ ID NO: 454-  
20 458 and 461-467) correspond to known sequences. Comparison of the determined

cDNA sequence of SEQ ID NO: 461 with sequences in the Genbank database using the BLAST program revealed homology to the previously identified transmembrane protease serine 2 (TMPRSS2). The full-length cDNA sequence for this clone is provided in SEQ ID NO: 751, with the corresponding amino acid sequence being  
5 provided in SEQ ID NO: 752. The cDNA sequence encoding the first 209 amino acids of TMPRSS2 is provided in SEQ ID NO: 753, with the first 209 amino acids being provided in SEQ ID NO: 754.

The sequence of SEQ ID NO: 462 (referred to as P835P) was found to correspond to the previously identified clone FLJ13518 (Accession AK023643; SEQ ID  
10 NO: 774), which had no associated open reading frame (ORF). This clone was used to search the Geneseq DNA database and matched a clone previously identified as a G protein-coupled receptor protein (DNA Geneseq Accession A09351; amino acid Geneseq Accession Y92365), that is characterized by the presence of seven transmembrane domains. The sequences of fragments between these domains are  
15 provided in SEQ ID NO: 778-785, with SEQ ID NO: 778, 780, 782 and 784 representing extracellular domains and SEQ ID NO: 779, 781, 783 and 785 representing intracellular domains. SEQ ID NO: 778-785 represent amino acids 1-28, 53-61, 83-103, 124-143, 165-201, 226-238, 263-272 and 297-381, respectively, of P835P. The full-length cDNA sequence for P835P is provided in SEQ ID NO: 773. The cDNA  
20 sequence of the open reading frame for P835P, including stop codon, is provided in SEQ ID NO: 775, with the open reading frame without stop codon being provided in SEQ ID NO: 776 and the corresponding amino acid sequence being provided in SEQ ID NO: 777.

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#### EXAMPLE 16

##### FURTHER CHARACTERIZATION OF PROSTATE-SPECIFIC ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P  
30 fragment described above. One million colonies were plated on LB/Ampicillin plates.

Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic Perkin Elmer/Applied Biosystems Division Sequencer. Four sequences were obtained, and are presented in SEQ ID NO: 468-471. These sequences appear to represent different splice variants of the P710P gene. Subsequent comparison of the cDNA sequences of P710P with those in Genbank revealed homology to the DD3 gene (Genbank accession numbers AF103907 & AF103908). The cDNA sequence of DD3 is provided in SEQ ID NO: 618.

#### EXAMPLE 17

##### PROTEIN EXPRESSION OF PROSTATE-SPECIFIC ANTIGENS

This example describes the expression and purification of prostate-specific antigens in *E. coli*, baculovirus, mammalian and yeast cells.

##### a) Expression of P501S in *E. coli*

Expression of the full-length form of P501S was attempted by first cloning P501S without the leader sequence (amino acids 36-553 of SEQ ID NO: 113) downstream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) in pET17b. Specifically, P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an antisense cloning primer that contains an EcoRI site. DNA amplification was performed using 5 µl 10X Pfu buffer, 1 µl 20 mM dNTPs, 1 µl each of the PCR primers at 10 µM concentration, 40 µl water, 1 µl Pfu DNA polymerase (Stratagene, La Jolla, CA) and 1 µl DNA at 100 ng/µl. Denaturation at 95°C was performed for 30 sec, followed by 10 cycles of 95°C for 30 sec, 60°C for 1 min and by 72°C for 3 min. 20 cycles of 95°C for 30 sec, 65°C for 1 min and by 72°C for 3 min, and lastly by 1 cycle of 72°C for 10 min. The PCR product was

cloned to Ra12m/pET17b using HindIII and EcoRI. The sequence of the resulting fusion construct (referred to as Ra12-P501S-F) was confirmed by DNA sequencing.

The fusion construct was transformed into BL21(DE3)pLysE, pLysS and CodonPlus *E. coli* (Stratagene) and grown overnight in LB broth with kanamycin. The  
5 resulting culture was induced with IPTG. Protein was transferred to PVDF membrane and blocked with 5% non-fat milk (in PBS-Tween buffer), washed three times and incubated with mouse anti-His tag antibody (Clontech) for 1 hour. The membrane was washed 3 times and probed with HRP-Protein A (Zymed) for 30 min. Finally, the membrane was washed 3 times and developed with ECL (Amersham). No expression  
10 was detected by Western blot. Similarly, no expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage (Invitrogen).

An N-terminal fragment of P501S (amino acids 36-325 of SEQ ID NO: 113) was cloned down-stream of the first 30 amino acids of the *M. tuberculosis* antigen  
15 Ra12 in pET17b as follows. P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an antisense cloning primer that contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The fusion construct (referred to as  
20 Ra12-P501S-N) was confirmed by DNA sequencing.

The Ra12-P501S-N fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, essentially as described above. Using Western blot analysis, protein bands were observed at the expected molecular weight of 36 kDa. Some high molecular weight bands were also observed, probably due to  
25 aggregation of the recombinant protein. No expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage.

A fusion construct comprising a C-terminal portion of P501S (amino acids 257-553 of SEQ ID NO: 113) located down-stream of the first 30 amino acids of  
30 the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) was prepared as follows. P501S

DNA was used to perform PCR using the primers AW026 (SEQ ID NO: 488) and AW003 (SEQ ID NO: 486). AW026 is a sense cloning primer that contains a HindIII site. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The  
5 sequence for the fusion construct (referred to as Ra12-P501S-C) was confirmed.

The Ra12-P501S-C fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, as described above. A small amount of protein was detected by Western blot, with some molecular weight aggregates also being observed. Expression was also detected by Western blot when the Ra12-P501S-C  
10 fusion was used for expression in BL21CodonPlus induced by CE6 phage.

A fusion construct comprising a fragment of P501S (amino acids 36-298 of SEQ ID NO: 113) located down-stream of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 705) was prepared as follows. P501S DNA was used to perform PCR using the primers AW042 (SEQ ID NO: 706) and AW053 (SEQ ID NO: 707). AW042 is a sense  
15 cloning primer that contains a EcoRI site. AW053 is an antisense primer with stop and Xho I sites. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the EcoRI and Xho I sites. The resulting fusion construct (referred to as Ra12-P501S-E2) was expressed in B834 (DE3) pLys *S. E. coli* host cells in TB media for 2 h at room temperature. Expressed protein  
20 was purified by washing the inclusion bodies and running on a Ni-NTA column. The purified protein stayed soluble in buffer containing 20 mM Tris-HCl (pH 8), 100 mM NaCl, 10 mM  $\beta$ -Me and 5% glycerol. The determined cDNA and amino acid sequences for the expressed fusion protein are provided in SEQ ID NO: 708 and 709, respectfully.

25 **b) Expression of P501S in Baculovirus**

The Bac-to-Bac baculovirus expression system (BRL Life Technologies, Inc.) was used to express P501S protein in insect cells. Full-length P501S (SEQ ID NO: 113) was amplified by PCR and cloned into the XbaI site of the donor plasmid pFastBacI. The recombinant bacmid and baculovirus were prepared according to the

manufacturer's instructions. The recombinant baculovirus was amplified in Sf9 cells and the high titer viral stocks were utilized to infect High Five cells (Invitrogen) to make the recombinant protein. The identity of the full-length protein was confirmed by N-terminal sequencing of the recombinant protein and by Western blot analysis (Figure 7). Specifically, 0.6 million High Five cells in 6-well plates were infected with either the unrelated control virus BV/ECD\_PD (lane 2), with recombinant baculovirus for P501S at different amounts or MOIs (lanes 4-8), or were uninfected (lane 3). Cell lysates were run on SDS-PAGE under reducing conditions and analyzed by Western blot with the anti-P501S monoclonal antibody P501S-10E3-G4D3 (prepared as described below). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

The localization of recombinant P501S in the insect cells was investigated as follows. The insect cells overexpressing P501S were fractionated into fractions of nucleus, mitochondria, membrane and cytosol. Equal amounts of protein from each fraction were analyzed by Western blot with a monoclonal antibody against P501S. Due to the scheme of fractionation, both nucleus and mitochondria fractions contain some plasma membrane components. However, the membrane fraction is basically free from mitochondria and nucleus. P501S was found to be present in all fractions that contain the membrane component, suggesting that P501S may be associated with plasma membrane of the insect cells expressing the recombinant protein.

#### c) Expression of P501S in Mammalian Cells

Full-length P501S (553 amino acids; SEQ ID NO: 113) was cloned into various mammalian expression vectors, including pCEP4 (Invitrogen), pVR1012 (Vical, San Diego, CA) and a modified form of the retroviral vector pBMN, referred to as pBIB. Transfection of P501S/pCEP4 and P501S/pVR1012 into HEK293 fibroblasts was carried out using the Fugene transfection reagent (Boehringer Mannheim). Briefly, 2 ul of Fugene reagent was diluted into 100 ul of serum-free media and incubated at room temperature for 5-10 min. This mixture was added to 1 ug of P501S plasmid DNA, mixed briefly and incubated for 30 minutes at room temperature. The

Fugene/DNA mixture was added to cells and incubated for 24-48 hours. Expression of recombinant P501S in transfected HEK293 fibroblasts was detected by means of Western blot employing a monoclonal antibody to P501S.

Transfection of p501S/pCEP4 into CHO-K cells (American Type Culture Collection, Rockville, MD) was carried out using GenePorter transfection reagent (Gene Therapy Systems, San Diego, CA). Briefly, 15  $\mu$ l of GenePorter was diluted in 500  $\mu$ l of serum-free media and incubated at room temperature for 10 min. The GenePorter/media mixture was added to 2  $\mu$ g of plasmid DNA that was diluted in 500  $\mu$ l of serum-free media, mixed briefly and incubated for 30 min at room temperature. CHO-K cells were rinsed in PBS to remove serum proteins, and the GenePorter/DNA mix was added and incubated for 5 hours. The transfected cells were then fed an equal volume of 2x media and incubated for 24-48 hours.

FACS analysis of P501S transiently infected CHO-K cells, demonstrated surface expression of P501S. Expression was detected using rabbit polyclonal antisera raised against a P501S peptide, as described below. Flow cytometric analysis was performed using a FaCScan (Becton Dickinson), and the data were analyzed using the Cell Quest program.

d) Expression of P501S in *S. cerevisiae*

P501S was expressed in yeast, directed in membranes, using the yeast  $\alpha$  prepro signal sequence. The natural signal sequence and first luminal domain of P501S was deleted in order to conserve the natural positioning of the expressed P501S protein.

Specifically, the  $\alpha$  prepro signal sequence of *S. cerevisiae* linked to amino acids 55-553 of SEQ ID NO: 113 with a His tag tail was cloned into the plasmid pRIT15068 with the CUP1 promoter and transfected into *S. cerevisiae* strain Y1790. The Y1790 strain is Leu<sup>+</sup> and His<sup>-</sup>. Expression of protein was induced by addition of either 500  $\mu$ M or 250  $\mu$ M of CuSO<sub>4</sub> at 30 °C in minimal medium supplemented with histidine. Cells were harvested 24 hours after induction. Extracts were prepared by growing cells to a concentration of OD600 5.0 in 50 mM citrate phosphate buffer (pH 4.0) plus 130 mM NaCl supplemented with protease inhibitors. Cells were disrupted

using glass beads and centrifuged for 20 min at 15,000 g. The recombinant protein was found to be 100% pellet associated.

Expression of the recombinant protein (molecular weight 63 kD) was demonstrated by Western blot analysis, using the anti-P501S monoclonal antibody 10E-D4-G3 described below. The amino acid sequence of the expressed protein is provided in SEQ ID NO: 792.

Fermentation processes for the production of the  $\alpha$  prepro-P501S-His tag recombinant protein in *S. cerevisiae* (strain Y1790 – CUP1 inducible promoter) were evaluated as follows. One hundred  $\mu$ l of a master seed containing  $2.5 \times 10^8$  cells/ml of transformed *S. cerevisiae* Y1790 were spread on FSC004AA solid medium. The composition of the FSC004AA medium is as follows: glucose 10 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  0.0002 g/l; folic acid 0.000064 g/l;  $\text{KH}_2\text{PO}_4$  1 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  0.0004 g/l; Inositol 0.064 g/l;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  0.5 g/l;  $\text{H}_3\text{BO}_3$  0.0005 g/l; Pyridoxine 0.008 g/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  0.00009 g/l; Niacin 0.000032 g/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  0.0004 g/l;  $(\text{NH}_4)_2\text{SO}_4$  5 g/l; agar 18 g/l; Histidine 0.1 g/l.

Two plates were incubated for 26 h at 30 °C. These solid pre-cultures were harvested in 5 ml of liquid medium FSC007AA and 0.5 ml (or  $9.3 \times 10^7$  cells) of this suspension was used to inoculate 2 liquid pre-cultures.

The composition of the FSC007AA medium is as follows: Glucose 10 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  0.0002 g/l; folic acid 0.000064 g/l;  $\text{KH}_2\text{PO}_4$  1 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  0.0004 g/l; Inositol 0.064 g/l;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  0.5 g/l;  $\text{H}_3\text{BO}_3$  0.0005 g/l; Pyridoxine 0.008 g/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  0.00009 g/l; Niacine 0.000032 g/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  0.0004 g/l;  $(\text{NH}_4)_2\text{SO}_4$  5 g/l; Histidine 0.1 g/l.

These pre-cultures were run for 20 hours in 2L flasks containing 400 ml of medium FSC007AA in order to obtain an OD of 1.8. The other characteristics of these pre-cultures are as follows: pH 2.8; glucose 2.3 g/L; ethanol 3.4 g/L.



The best timing for liquid pre-cultures for strain Y1790 was determined in preliminary experiments. Liquid pre-cultures containing 400 ml of medium and inoculated with various volumes of Master Seed (0.25, 0.5, 1 or 2 ml) were monitored in order to identify the best inoculum size and timing. Glucose, ethanol, pH, OD and cell number (determined by flow cytometry) were followed between 16 and 23 hours of culture. Glucose exhaustion and maximal biomass were obtained after 20 hour incubation with 0.5 inoculum. These conditions were adopted for transferring the pre-culture into fermentation.

In total, 800ml of pre-culture were used to inoculate a 20 L fermenter containing 5L of medium FSC002AA. Three ml of irradiated antifoam were added before inoculation. The composition of the FSC002AA medium is as follows:  $(\text{NH}_4)_2\text{SO}_4$  6.4 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  2.05 mg/l; folic acid 0.54 mg/l;  $\text{KH}_2\text{PO}_4$  8.25 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  4.1 mg/l; inositol 540 mg;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  4.69 g/l;  $\text{H}_3\text{BO}_3$  5.17 m/l; pyridoxine 68 mg/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.92 g/l; KI 1.03 mg/l; thiamine 68 mg/l; NaCl 0.06g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  0.92 mg/l; Niacine 0.27 mg/l; HCl 1 ml/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  9.92 mg/l; Riboflavin 0.13 mg/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  0.41 mg/l; Glucose 0.14 g/l; Panthotenate Ca 68 mg/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  4.1 mg/l; Biotin 0.54 mg/l; para-aminobenzoic acid 0.13 mg/l; Histidine 0.3 g/l

The carbon source (glucose) was supplemented by a continuous feeding of FFB004AA medium. The composition of the FFB004AA medium is as follows: glucose 350 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  5.15 mg/l; folic acid 1.36 mg/l;  $\text{KH}_2\text{PO}_4$  20.6 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  10.3 mg/l; inositol 1350 mg/l;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  11.7 g/l;  $\text{H}_3\text{BO}_3$  12.9 m/l; pyridoxine 170 mg/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  2.35 g/l; KI 2.6 mg/l; thiamine 170 g/l; NaCl 0.15 g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  2.3 mg/l; niacine 0.67 mg/l; HCl 2.5 ml/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  24.8 mg/l; riboflavin; 0.33 mg/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  1.03 mg/l; biotin 1.36 mg/l; panthotenate Ca 170 mg/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  10.3 mg/l; para-aminobenzoic acid: 0.33 mg/l; histidine 5.35 g/l.

The residual glucose concentration was maintained very low ( $\square 50$  mg/L) in order to minimize ethanol production by fermentation. This was achieved by limiting the development of the microorganism using a limited glucose feed rate. The Standard biomass content (OD 80-90) was reached in fermentation after 44 hour growth phase.

CUP1 promoter was then induced by adding 500 $\mu$ M  $\text{CuSO}_4$  in order to

produce P501S antigen.  $\text{CuSO}_4$  addition was followed by ethanol accumulation (up to 6 g/L), and the glucose feeding rate was then reduced in order to consume the ethanol. The copper available for the microorganism was monitored by testing Cu ion concentration in the broth supernatant using a spectrophotometric copper assay (DETC method). The fermentation was then supplemented by  $\text{CuSO}_4$  throughout the induction phase in order to maintain its concentration between 150 and 250  $\mu\text{M}$  in the supernatant. The biomass reached an OD of 100 at the end of induction. Cells were harvested after 8 hours of induction.

Cell homogenate was prepared and analysed by SDS-PAGE and Western Blot using standard protocols. A major protein band with the expected molecular weight of 62KD was detected by Western blot using anti-P501S monoclonal antibodies. Western blot analysis also showed that the major 62KD band was progressively produced from 30 minutes of induction on, and reached a maximum after 3 hours. No more antigen seemed to be produced between 3 and 12 hours of induction.

The number of passages through a French Press necessary to extract all the antigen from the cells was evaluated. One, three and five passages were tested and total cell lysates, supernatants and pellets of cell lysates were analysed by Western blot. Three passages through a French Press were sufficient to completely extract the antigen. The antigen was present in the insoluble fraction.

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#### e) Expression of P703P in Baculovirus

The cDNA for full-length P703P-DE5 (SEQ ID NO: 326), together with several flanking restriction sites, was obtained by digesting the plasmid pCDNA703 with restriction endonucleases Xba I and Hind III. The resulting restriction fragment (approx. 800 base pairs) was ligated into the transfer plasmid pFastBacI which was digested with the same restriction enzymes. The sequence of the insert was confirmed by DNA sequencing. The recombinant transfer plasmid pFBP703 was used to make recombinant bacmid DNA and baculovirus using the Bac-To-Bac Baculovirus expression system (BRL Life Technologies). High Five cells were infected with the recombinant virus BVP703, as described above, to obtain recombinant P703P protein.

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e) Expression of P788P in *E. Coli*

A truncated, N-terminal portion, of P788P (residues 1-644 of SEQ ID NO: 777; referred to as P788P-N) fused with a C-terminal 6xHis Tag was expressed in *E. coli* as follows. P788P cDNA was amplified using the primers AW080 and AW081 (SEQ ID NO: 672 and 673). AW080 is a sense cloning primer with an NdeI site. AW081 is an antisense cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and XhoI. Vector and insert were ligated and transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. P788P-N clone #6 was confirmed to be identical to the designed construct. The expression construct P788P-N #6/pCRX1 was transformed into *E. coli* BL21 CodonPlus-RIL competent cells. After induction, most of the cells grew well, achieving OD600 of greater than 2.0 after 3 hr. Coomassie stained SDS-PAGE showed an over-expressed band at about 75 kD. Western blot analysis using a 6xHisTag antibody confirmed the band was P788P-N. The determined cDNA sequence for P788P-N is provided in SEQ ID NO: 674, with the corresponding amino acid sequence being provided in SEQ ID NO: 675.

f) Expression of P510S in *E. Coli*

The P510S protein has 9 potential transmembrane domains and is predicted to be located at the plasma membrane. The C-terminal protein of this protein, as well as the predicted third extracellular domain of P510S were expressed in *E. coli* as follows.

The expression construct referred to as Ra12-P501S-C was designed to have a 6 HisTag at the N-terminal end, followed by the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and then the C-terminal portion of P510S (amino residues 1176-1261 of SEQ ID NO: 538). Full-length P510S was used to amplify the P510S-C fragment by PCR using the primers AW056 and AW057 (SEQ ID NO: 677 and 678, respectively). AW056 is a sense cloning primer with an EcoRI site. AW057 is an antisense primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then purified. The insert and

vector were ligated together and transformed into NovaBlue. Colonies were randomly screened for insert and sequences. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. A mini-induction screen was performed to optimize the expression conditions. After induction  
5 the cells grew well, achieving OD 600 nm greater than 2.0 after 3 hours. Coomassie stain SDS-PAGE showed a highly over-expressed band at approx. 30 kD. Though this is higher than the expected molecular weight, western blot analysis was positive, showing this band to be the His tag-containing protein. The optimized culture conditions are as follows. Dilute overnight culture/daytime culture (LB + kanamycin +  
10 chloramphenicol) into 2xYT (with kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2xYT. Allow to grow at 37 °C until OD600 = 0.6. Take an aliquot out as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3 sample, spin down cells and store at -80 °C. The determined cDNA and amino acid sequences for the Ra12-P510S-C construct are provided in SEQ ID NO: 679 and 682,  
15 respectively.

The expression construct P510S-C was designed to have a 5' added start codon and a glycine (GGA) codon and then the P510S C terminal fragment followed by the in frame 6x histidine tag and stop codon from the pET28b vector. The cloning strategy is similar to that used for Ra12-P510S-C, except that the PCR primers employed were  
20 those shown in SEQ ID NO: 685 and 686, respectively and the NcoI/XhoI cut in pET28b was used. The primer of SEQ ID NO: 685 created a 5' NcoI site and added a start codon. The antisense primer of SEQ ID NO: 686 creates a XhoI site on P510S C terminal fragment. Clones were confirmed by sequencing. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL  
25 competent cells. An OD600 of greater than 2.0 was obtained 30 hours after induction. Coomassie stained SDS-PAGE showed an over-expressed band at about 11 kD. Western blot analysis confirmed that the band was P510S-C, as did N-terminal protein sequencing. The optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (+ kanamycin  
30 and chloramphenicol) at a ratio of 25 mL culture to 1 liter 2x YT, and allow to grow at

37 °C until an OD 600 of about 0.5 is reached. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P510S-C construct are shown in SEQ ID NO: 680 and 683, respectively.

5                   The predicted third extracellular domain of P510S (P510S-E3; residues 328-676 of SEQ ID NO: 538) was expressed in *E. coli* as follows. The P510S fragment was amplified by PCR using the primers shown in SEQ ID NO: 687 and 688. The primer of SEQ ID NO: 687 is a sense primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 688 is an antisense primer with an added XhoI site  
10 for use in ligating into pPDM. The resulting fragment was cloned to pPDM at the NdeI and XhoI sites. Clones were confirmed by sequencing. For protein expression, the clone was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. After induction, an OD600 of greater than 2.0 was achieved after 3 hours. Coomassie stained SDS-PAGE showed an over-expressed band at about 39 kD, and N-terminal sequencing  
15 confirmed the N-terminal to be that of P510S-E3. Optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2x YT. Allow to grow at 37 °C until OD 600 equals 0.6. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3  
20 sample, spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P501S-E3 construct are provided in SEQ ID NO: 681 and 684, respectively.

g) Expression of P775S in *E. Coli*

25                   The antigen P775P contains multiple open reading frames (ORF). The third ORF, encoding the protein of SEQ ID NO: 483, has the best emotif score. An expression fusion construct containing the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and P775P-ORF3 with an N-terminal 6x HisTag was prepared as follows. P775P-ORF3 was amplified using the sense PCR primers of SEQ ID NO: 689 and the anti-sense PCR primer of SEQ ID NO: 690. The PCR amplified fragment of P775P and

Ra12/pCRX1 were digested with the restriction enzymes EcoRI and XhoI. Vector and insert were ligated and then transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. A clone having the desired sequence was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. Two hours after  
5 induction, the cell density peaked at OD600 of approximately 1.8. Coomassie stained SDS-PAGE showed an over-expressed band at about 31 kD. Western blot using 6x HisTag antibody confirmed that the band was Ra12-P775P-ORF3. The determined cDNA and amino acid sequences for the fusion construct are provided in SEQ ID NO: 691 and 692, respectively.

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#### H) EXPRESSION OF A P703P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P703P was prepared by PCR using the primers of SEQ ID NO: 693 and 694. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag  
15 in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P703P are provided in SEQ ID NO: 695 and 696, respectively.

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#### I) EXPRESSION OF A P705P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P705P was prepared by PCR using the primers of SEQ ID NO: 697 and 698. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag  
25 in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P705P are provided in SEQ ID NO: 699 and 700, respectively.

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**J) EXPRESSION OF A P711P HIS TAG FUSION PROTEIN IN E. COLI**

The cDNA for the coding region of P711P was prepared by PCR using the primers of SEQ ID NO: 701 and 702. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco2I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P711P are provided in SEQ ID NO: 703 and 704, respectively.

**EXAMPLE 18****PREPARATION AND CHARACTERIZATION OF ANTIBODIES  
AGAINST PROSTATE-SPECIFIC POLYPEPTIDES****a) Preparation and Characterization of Polyclonal Antibodies against P703P,  
P504S and P509S**

Polyclonal antibodies against P703P, P504S and P509S were prepared as follows.

Each prostate tumor antigen expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run

through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin such as HiPrepQ (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The proteins were then vialled after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4°C for 12-4 hours followed by centrifugation.

Ninety-six well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 microliters of BSA blocking buffer was added to the wells and incubated at room



temperature for 2 hours. Plates were washed 6 times with PBS/0.01 % Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H<sub>2</sub>SO<sub>4</sub> and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

**b) Preparation and Characterization of Antibodies against P501S**

A murine monoclonal antibody directed against the carboxy-terminus of the prostate-specific antigen P501S was prepared as follows.

A truncated fragment of P501S (amino acids 355-526 of SEQ ID NO: 113) was generated and cloned into the pET28b vector (Novagen) and expressed in *E. coli* as a thioredoxin fusion protein with a histidine tag. The trx-P501S fusion protein was purified by nickel chromatography, digested with thrombin to remove the trx fragment and further purified by an acid precipitation procedure followed by reverse phase HPLC.

Mice were immunized with truncated P501S protein. Serum bleeds from mice that potentially contained anti-P501S polyclonal sera were tested for P501S-specific reactivity using ELISA assays with purified P501S and trx-P501S proteins. Serum bleeds that appeared to react specifically with P501S were then screened for P501S reactivity by Western analysis. Mice that contained a P501S-specific antibody component were sacrificed and spleen cells were used to generate anti-P501S antibody producing hybridomas using standard techniques. Hybridoma supernatants were tested for P501S-specific reactivity initially by ELISA, and subsequently by FACS analysis of reactivity with P501S transduced cells. Based on these results, a monoclonal hybridoma referred to as 10E3 was chosen for further subcloning. A number of subclones were

generated, tested for specific reactivity to P501S using ELISA and typed for IgG isotype. The results of this analysis are shown below in Table V. Of the 16 subclones tested, the monoclonal antibody 10E3-G4-D3 was selected for further study.

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Table V

Isotype analysis of murine anti-P501S monoclonal antibodies

Hybridoma clone	Isotype	Estimated [Ig] in supernatant ( $\mu\text{g/ml}$ )
4D11	IgG1	14.6
1G1	IgG1	0.6
4F6	IgG1	72
4H5	IgG1	13.8
4H5-E12	IgG1	10.7
4H5-EH2	IgG1	9.2
4H5-H2-A10	IgG1	10
4H5-H2-A3	IgG1	12.8
4H5-H2-A10-G6	IgG1	13.6
4H5-H2-B11	IgG1	12.3
10E3	IgG2a	3.4
10E3-D4	IgG2a	3.8
10E3-D4-G3	IgG2a	9.5
10E3-D4-G6	IgG2a	10.4
10E3-E7	IgG2a	6.5
8H12	IgG2a	0.6

The specificity of 10E3-G4-D3 for P501S was examined by FACS analysis. Specifically, cells were fixed (2% formaldehyde, 10 minutes), permeabilized (0.1% saponin, 10 minutes) and stained with 10E3-G4-D3 at 0.5 – 1  $\mu\text{g/ml}$ , followed by incubation with a secondary, FITC-conjugated goat anti-mouse Ig antibody (Pharmingen, San Diego, CA). Cells were then analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. For analysis of infected cells, B-LCL were infected with a vaccinia vector that expresses P501S. To demonstrate specificity in these assays, B-LCL transduced with a different antigen (P703P) and uninfected B-LCL vectors were utilized. 10E3-G4-D3 was shown to bind with P501S-transduced B-

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LCL and also with P501S-infected B-LCL, but not with either uninfected cells or P703P-transduced cells.

To determine whether the epitope recognized by 10E3-G4-D3 was found on the surface or in an intracellular compartment of cells, B-LCL were transduced with  
5 P501S or HLA-B8' as a control antigen and either fixed and permeabilized as described above or directly stained with 10E3-G4-D3 and analyzed as above. Specific recognition of P501S by 10E3-G4-D3 was found to require permeabilization, suggesting that the epitope recognized by this antibody is intracellular.

The reactivity of 10E3-G4-D3 with the three prostate tumor cell lines  
10 Lncap, PC-3 and DU-145, which are known to express high, medium and very low levels of P501S, respectively, was examined by permeabilizing the cells and treating them as described above. Higher reactivity of 10E3-G4-D3 was seen with Lncap than with PC-3, which in turn showed higher reactivity than DU-145. These results are in agreement with the real time PCR and demonstrate that the antibody specifically  
15 recognizes P501S in these tumor cell lines and that the epitope recognized in prostate tumor cell lines is also intracellular.

Specificity of 10E3-G4-D3 for P501S was also demonstrated by Western blot analysis. Lysates from the prostate tumor cell lines Lncap, DU-145 and PC-3, from P501S-transiently transfected HEK293 cells, and from non-transfected HEK293 cells  
20 were generated. Western blot analysis of these lysates with 10E3-G4-D3 revealed a 46 kDa immunoreactive band in Lncap, PC-3 and P501S-transfected HEK cells, but not in DU-145 cells or non-transfected HEK293 cells. P501S mRNA expression is consistent with these results since semi-quantitative PCR analysis revealed that P501S mRNA is expressed in Lncap, to a lesser but detectable level in PC-3 and not at all in DU-145  
25 cells. Bacterially expressed and purified recombinant P501S (referred to as P501SStr2) was recognized by 10E3-G4-D3 (24 kDa), as was full-length P501S that was transiently expressed in HEK293 cells using either the expression vector VR1012 or pCEP4. Although the predicted molecular weight of P501S is 60.5 kDa, both transfected and "native" P501S run at a slightly lower mobility due to its hydrophobic nature.

Immunohistochemical analysis was performed on prostate tumor and a panel of normal tissue sections (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). Tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and incubated with 10E3-G4-D3 antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize P501S immunoreactivity. P501S was found to be highly expressed in both normal prostate and prostate tumor tissue but was not detected in any of the other tissues tested.

To identify the epitope recognized by 10E3-G4-D3, an epitope mapping approach was pursued. A series of 13 overlapping 20-21 mers (5 amino acid overlap; SEQ ID NO: 489-501) was synthesized that spanned the fragment of P501S used to generate 10E3-G4-D3. Flat bottom 96 well microtiter plates were coated with either the peptides or the P501S fragment used to immunize mice, at 1 microgram/ml for 2 hours at 37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified antibody 10E3-G4-D3 was added at 2 fold dilutions (1000 ng – 16 ng) in PBST and incubated for 30 minutes at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti-mouse IgG (H+L) Affinipure F(ab') fragment (Jackson ImmunoResearch, West Grove, PA) at 1:20000 for 30 minutes. Plates were then washed and incubated for 15 minutes in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 8, reactivity was seen with the peptide of SEQ ID NO: 496 (corresponding to amino acids 439-459 of P501S) and with the P501S fragment but not with the remaining peptides, demonstrating that the epitope recognized by 10E3-G4-D3 is localized to amino acids 439-459 of SEQ ID NO: 113.

In order to further evaluate the tissue specificity of P501S, multi-array immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from

these tissues. Sixty-five of these human tissue samples were of prostate origin. Tissue sections 0.6 mm in diameter were formalin-fixed and paraffin embedded. Samples were pretreated with HIER using 10 mM citrate buffer pH 6.0 and boiling for 10 min. Sections were stained with 10E3-G4-D3 and P501S immunoreactivity was visualized with HRP. All the 65 prostate tissues samples (5 normal, 55 untreated prostate tumors, 5 hormone refractory prostate tumors) were positive, showing distinct perinuclear staining. All other tissues examined were negative for P501S expression.

**c) Preparation and Characterization of Antibodies against P503S**

10. A fragment of P503S (amino acids 113-241 of SEQ ID NO: 114) was expressed and purified from bacteria essentially as described above for P501S and used to immunize both rabbits and mice. Mouse monoclonal antibodies were isolated using standard hybridoma technology as described above. Rabbit monoclonal antibodies were isolated using Selected Lymphocyte Antibody Method (SLAM) technology at
- 15 Immgenics Pharmaceuticals (Vancouver, BC, Canada). Table VI, below, lists the monoclonal antibodies that were developed against P503S.

**Table VI**

Antibody	Species
20D4	Rabbit
JA1	Rabbit
1A4	Mouse
1C3	Mouse
1C9	Mouse
1D12	Mouse
2A11	Mouse
2H9	Mouse
4H7	Mouse
8A8	Mouse
8D10	Mouse
9C12	Mouse
6D12	Mouse

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 20D4 and JA1 were determined and are provided in SEQ ID NO: 502 and 503, respectively.

5           In order to better define the epitope binding region of each of the antibodies, a series of overlapping peptides were generated that span amino acids 109-213 of SEQ ID NO: 114. These peptides were used to epitope map the anti-P503S monoclonal antibodies by ELISA as follows. The recombinant fragment of P503S that was employed as the immunogen was used as a positive control. Ninety-six well  
10   microtiter plates were coated with either peptide or recombinant antigen at 20 ng/well overnight at 4 °C. Plates were aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature then washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit monoclonal antibodies diluted in PBST were added to the wells and incubated for 30 min at room temperature. This was  
15   followed by washing 6 times with PBST and incubation with Protein-A HRP conjugate at a 1:2000 dilution for a further 30 min. Plates were washed six times in PBST and incubated with tetramethylbenzidine (TMB) substrate for a further 15 min. The reaction was stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using at ELISA plate reader. ELISA with the mouse monoclonal antibodies was performed with  
20   supernatants from tissue culture run neat in the assay.

All of the antibodies bound to the recombinant P503S fragment, with the exception of the negative control SP2 supernatant. 20D4, JA1 and 1D12 bound strictly to peptide #2101 (SEQ ID NO: 504), which corresponds to amino acids 151-169 of SEQ ID NO: 114. 1C3 bound to peptide #2102 (SEQ ID NO: 505), which corresponds  
25   to amino acids 165-184 of SEQ ID NO: 114. 9C12 bound to peptide #2099 (SEQ ID NO: 522), which corresponds to amino acids 120-139 of SEQ ID NO: 114. The other antibodies bind to regions that were not examined in these studies.

Subsequent to epitope mapping, the antibodies were tested by FACS analysis on a cell line that stably expressed P503S to confirm that the antibodies bind to  
30   cell surface epitopes. Cells stably transfected with a control plasmid were employed as

a negative control. Cells were stained live with no fixative. 0.5 ug of anti-P503S monoclonal antibody was added and cells were incubated on ice for 30 min before being washed twice and incubated with a FITC-labelled goat anti-rabbit or mouse secondary antibody for 20 min. After being washed twice, cells were analyzed with an Excalibur  
5 fluorescent activated cell sorter. The monoclonal antibodies 1C3, 1D12, 9C12, 20D4 and JA1, but not 8D3, were found to bind to a cell surface epitope of P503S.

In order to determine which tissues express P503S, immunohistochemical analysis was performed, essentially as described above, on a panel of normal tissues (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder,  
10 ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). HRP-labeled anti-mouse or anti-rabbit antibody followed by incubation with TMB was used to visualize P503S immunoreactivity. P503S was found to be highly expressed in prostate tissue, with lower levels of expression being observed in cervix, colon, ileum and kidney, and no expression being observed in adrenal, breast, duodenum, gall  
15 bladder, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis.

Western blot analysis was used to characterize anti-P503S monoclonal antibody specificity. SDS-PAGE was performed on recombinant (rec) P503S expressed in and purified from bacteria and on lysates from HEK293 cells transfected with full length P503S. Protein was transferred to nitrocellulose and then Western blotted with  
20 each of the anti-P503S monoclonal antibodies (20D4, JA1, 1D12, 6D12 and 9C12) at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to either a goat anti-mouse monoclonal antibody or to protein A-sepharose. The monoclonal antibody 20D4 detected the appropriate molecular weight 14 kDa recombinant P503S (amino acids 113-241) and the 23.5 kDa  
25 species in the HEK293 cell lysates transfected with full length P503S. Other anti-P503S monoclonal antibodies displayed similar specificity by Western blot.

#### d) Preparation and Characterization of Antibodies against P703P

Rabbits were immunized with either a truncated (P703Ptr1; SEQ ID NO: 172) or full-length mature form (P703Pfl; SEQ ID NO: 523) of recombinant P703P

protein was expressed in and purified from bacteria as described above. Affinity purified polyclonal antibody was generated using immunogen P703Pfl or P703Ptrl attached to a solid support. Rabbit monoclonal antibodies were isolated using SLAM technology at Immgenics Pharmaceuticals. Table VII below lists both the polyclonal and monoclonal antibodies that were generated against P703P.

Table VII

Antibody	Immunogen	Species/type
Aff. Purif. P703P (truncated); #2594	P703Ptrl	Rabbit polyclonal
Aff. Purif. P703P (full length); #9245	P703Pfl	Rabbit polyclonal
2D4	P703Ptrl	Rabbit monoclonal
8H2	P703Ptrl	Rabbit monoclonal
7H8	P703Ptrl	Rabbit monoclonal

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 8H2, 7H8 and 2D4 were determined and are provided in SEQ ID NO: 506-508, respectively.

Epitope mapping studies were performed as described above. Monoclonal antibodies 2D4 and 7H8 were found to specifically bind to the peptides of SEQ ID NO: 509 (corresponding to amino acids 145-159 of SEQ ID NO: 172) and SEQ ID NO: 510 (corresponding to amino acids 11-25 of SEQ ID NO: 172), respectively. The polyclonal antibody 2594 was found to bind to the peptides of SEQ ID NO: 511-514, with the polyclonal antibody 9427 binding to the peptides of SEQ ID NO: 515-517.

The specificity of the anti-P703P antibodies was determined by Western blot analysis as follows. SDS-PAGE was performed on (1) bacterially expressed recombinant antigen; (2) lysates of HEK293 cells and Ltk<sup>-/-</sup> cells either untransfected or transfected with a plasmid expressing full length P703P; and (3) supernatant isolated from these cell cultures. Protein was transferred to nitrocellulose and then Western blotted using the anti-P703P polyclonal antibody #2594 at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to an anti-rabbit antibody. A 35 kDa immunoreactive band could be observed with



recombinant P703P. Recombinant P703P runs at a slightly higher molecular weight since it is epitope tagged. In lysates and supernatants from cells transfected with full length P703P, a 30 kDa band corresponding to P703P was observed. To assure specificity, lysates from HEK293 cells stably transfected with a control plasmid were also tested and were negative for P703P expression. Other anti-P703P antibodies showed similar results.

Immunohistochemical studies were performed as described above, using anti-P703P monoclonal antibody. P703P was found to be expressed at high levels in normal prostate and prostate tumor tissue but was not detectable in all other tissues tested (breast tumor, lung tumor and normal kidney).

e) Preparation and Characterization of Antibodies against P504S

Full-length P504S (SEQ ID NO: 108) was expressed and purified from bacteria essentially as described above for P501S and employed to raise rabbit monoclonal antibodies using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). The anti-P504S monoclonal antibody 13H4 was shown by Western blot to bind to both expressed recombinant P504S and to native P504S in tumor cells.

Immunohistochemical studies using 13H4 to assess P504S expression in various prostate tissues were performed as described above. A total of 104 cases, including 65 cases of radical prostatectomies with prostate cancer (PC), 26 cases of prostate biopsies and 13 cases of benign prostate hyperplasia (BPH), were stained with the anti-P504S monoclonal antibody 13H4. P504S showed strongly cytoplasmic granular staining in 64/65 (98.5%) of PCs in prostatectomies and 26/26 (100%) of PCs in prostatic biopsies. P504S was stained strongly and diffusely in carcinomas (4+ in 91.2% of cases of PC; 3+ in 5.5%; 2+ in 2.2% and 1+ in 1.1%) and high grade prostatic intraepithelial neoplasia (4+ in all cases). The expression of P504S did not vary with Gleason score. Only 17/91 (18.7%) of cases of NP/BPH around PC and 2/13 (15.4%) of BPH cases were focally (1+, no 2+ to 4+ in all cases) and weakly positive for P504S in large glands. Expression of P504S was not found in small atrophic glands, postatrophic hyperplasia, basal cell hyperplasia and transitional cell metaplasia in either biopsies or

prostatectomies. P504S was thus found to be over-expressed in all Gleason scores of prostate cancer (98.5 to 100% of sensitivity) and exhibited only focal positivities in large normal glands in 19/104 of cases (82.3% of specificity). These findings indicate that P504S may be usefully employed for the diagnosis of prostate cancer.

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### EXAMPLE 19

#### CHARACTERIZATION OF CELL SURFACE EXPRESSION AND CHROMOSOME LOCALIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

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This example describes studies demonstrating that the prostate-specific antigen P501S is expressed on the surface of cells, together with studies to determine the probable chromosomal location of P501S.

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The protein P501S (SEQ ID NO: 113) is predicted to have 11 transmembrane domains. Based on the discovery that the epitope recognized by the anti-P501S monoclonal antibody 10E3-G4-D3 (described above in Example 17) is intracellular, it was predicted that following transmembrane determinants would allow the prediction of extracellular domains of P501S. Fig. 9 is a schematic representation of the P501S protein showing the predicted location of the transmembrane domains and the intracellular epitope described in Example 17. Underlined sequence represents the predicted transmembrane domains, bold sequence represents the predicted extracellular domains, and italicized sequence represents the predicted intracellular domains. Sequence that is both bold and underlined represents sequence employed to generate polyclonal rabbit serum. The location of the transmembrane domains was predicted using HHMTOP as described by Tusnady and Simon (Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction, *J. Mol. Biol.* 283:489-506, 1998).

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Based on Fig. 9, the P501S domain flanked by the transmembrane domains corresponding to amino acids 274-295 and 323-342 is predicted to be extracellular. The peptide of SEQ ID NO: 518 corresponds to amino acids 306-320 of P501S and lies in the predicted extracellular domain. The peptide of SEQ ID NO: 519,

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which is identical to the peptide of SEQ ID NO: 518 with the exception of the substitution of the histidine with an asparagine, was synthesized as described above. A Cys-Gly was added to the C-terminus of the peptide to facilitate conjugation to the carrier protein. Cleavage of the peptide from the solid support was carried out using the following cleavage mixture: trifluoroacetic acid:ethanediol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for two hours, the peptide was precipitated in cold ether. The peptide pellet was then dissolved in 10% v/v acetic acid and lyophilized prior to purification by C18 reverse phase hplc. A gradient of 5-60% acetonitrile (containing 0.05% TFA) in water (containing 0.05% TFA) was used to elute the peptide. The purity of the peptide was verified by hplc and mass spectrometry, and was determined to be >95%. The purified peptide was used to generate rabbit polyclonal antisera as described above.

Surface expression of P501S was examined by FACS analysis. Cells were stained with the polyclonal anti-P501S peptide serum at 10 µg/ml, washed, incubated with a secondary FITC-conjugated goat anti-rabbit Ig antibody (ICN), washed and analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. To demonstrate specificity in these assays, B-LCL transduced with an irrelevant antigen (P703P) or nontransduced were stained in parallel. For FACS analysis of prostate tumor cell lines, Lncap, PC-3 and DU-145 were utilized. Prostate tumor cell lines were dissociated from tissue culture plates using cell dissociation medium and stained as above. All samples were treated with propidium iodide (PI) prior to FACS analysis, and data was obtained from PI-excluding (*i.e.*, intact and non-permeabilized) cells. The rabbit polyclonal serum generated against the peptide of SEQ ID NO: 519 was shown to specifically recognize the surface of cells transduced to express P501S, demonstrating that the epitope recognized by the polyclonal serum is extracellular.

To determine biochemically if P501S is expressed on the cell surface, peripheral membranes from Lncap cells were isolated and subjected to Western blot analysis. Specifically, Lncap cells were lysed using a dounce homogenizer in 5 ml of homogenization buffer (250 mM sucrose, 10 mM HEPES, 1mM EDTA, pH 8.0, 1

complete protease inhibitor tablet (Boehringer Mannheim)). Lysate samples were spun at 1000 g for 5 min at 4 °C. The supernatant was then spun at 8000g for 10 min at 4 °C. Supernatant from the 8000g spin was recovered and subjected to a 100,000g spin for 30 min at 4 °C to recover peripheral membrane. Samples were then separated by SDS-  
5 PAGE and Western blotted with the mouse monoclonal antibody 10E3-G4-D3 (described above in Example 17) using conditions described above. Recombinant purified P501S, as well as HEK293 cells transfected with and over-expressing P501S were included as positive controls for P501S detection. LCL cell lysate was included as a negative control. P501S could be detected in Lncap total cell lysate, the 8000g  
10 (internal membrane) fraction and also in the 100,000g (plasma membrane) fraction. These results indicate that P501S is expressed at, and localizes to, the peripheral membrane.

To demonstrate that the rabbit polyclonal antiserum generated to the peptide of SEQ ID NO: 519 specifically recognizes this peptide as well as the  
15 corresponding native peptide of SEQ ID NO: 518, ELISA analyses were performed. For these analyses, flat-bottomed 96 well microtiter plates were coated with either the peptide of SEQ ID NO: 519, the longer peptide of SEQ ID NO: 520 that spans the entire predicted extracellular domain, the peptide of SEQ ID NO: 521 which represents the epitope recognized by the P501S-specific antibody 10E3-G4-D3, or a P501S fragment  
20 (corresponding to amino acids 355-526 of SEQ ID NO: 113) that does not include the immunizing peptide sequence, at 1 µg/ml for 2 hours at 37 °C. Wells were aspirated, blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified anti-P501S polyclonal rabbit serum was added at 2 fold dilutions (1000 ng -  
25 125 ng) in PBST and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubating with HRP-conjugated goat anti-rabbit IgG (H+L) Affinipure F(ab') fragment at 1:20000 for 30 min. Plates were then washed and incubated for 15 min in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As  
30 shown in Fig. 11, the anti-P501S polyclonal rabbit serum specifically recognized the

peptide of SEQ ID NO: 519 used in the immunization as well as the longer peptide of SEQ ID NO: 520, but did not recognize the irrelevant P501S-derived peptides and fragments.

In further studies, rabbits were immunized with peptides derived from the P501S sequence and predicted to be either extracellular or intracellular, as shown in Fig. 9. Polyclonal rabbit sera were isolated and polyclonal antibodies in the serum were purified, as described above. To determine specific reactivity with P501S, FACS analysis was employed, utilizing either B-LCL transduced with P501S or the irrelevant antigen P703P, of B-LCL infected with vaccinia virus-expressing P501S. For surface expression, dead and non-intact cells were excluded from the analysis as described above. For intracellular staining, cells were fixed and permeabilized as described above. Rabbit polyclonal serum generated against the peptide of SEQ ID NO: 548, which corresponds to amino acids 181-198 of P501S, was found to recognize a surface epitope of P501S. Rabbit polyclonal serum generated against the peptide SEQ ID NO: 551, which corresponds to amino acids 543-553 of P501S, was found to recognize an epitope that was either potentially extracellular or intracellular since in different experiments intact or permeabilized cells were recognized by the polyclonal sera. Based on similar deductive reasoning, the sequences of SEQ ID NO: 541-547, 549 and 550, which correspond to amino acids 109-122, 539-553, 509-520, 37-54, 342-359, 295-323, 217-274, 143-160 and 75-88, respectively, of P501S, can be considered to be potential surface epitopes of P501S recognized by antibodies.

In further studies, mouse monoclonal antibodies were raised against amino acids 296 to 322 to P501S, which are predicted to be in an extracellular domain. A/J mice were immunized with P501S/adenovirus, followed by subsequent boosts with an *E. coli* recombinant protein, referred to as P501N, that contains amino acids 296 to 322 of P501S, and with peptide 296-322 (SEQ ID NO: 755) coupled with KLH. The mice were subsequently used for splenic B cell fusions to generate anti-peptide hybridomas. The resulting 3 clones, referred to as 4F4 (IgG1,kappa), 4G5 (IgG2a,kappa) and 9B9 (IgG1,kappa), were grown for antibody production. The 4G5 mAb was purified by passing the supernatant over a Protein A-sepharose column,

followed by antibody elution using 0.2M glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8, and buffer exchanged into PBS.

For ELISA analysis, 96 well plates were coated with P501S peptide 296-322 (referred to as P501-long), an irrelevant P775 peptide, P501S-N, P501TR2, P501S-long-KLH, P501S peptide 306-319 (referred to as P501-short)-KLH, or the irrelevant peptide 2073-KLH, all at a concentration of 2 ug/ml and allowed to incubate for 60 minutes at 37 °C. After coating, plates were washed 5X with PBS + 0.1% Tween and then blocked with PBS, 0.5% BSA, 0.4% Tween20 for 2 hours at room temperature. Following the addition of supernatants or purified mAb, the plates were incubated for 60 minutes at room temperature. Plates were washed as above and donkey anti-mouse IgHRP-linked secondary antibody was added and incubated for 30 minutes at room temperature, followed by a final washing as above. TMB peroxidase substrate was added and incubated 15 minutes at room temperature in the dark. The reaction was stopped by the addition of 1N H<sub>2</sub>SO<sub>4</sub> and the OD was read at 450 nM. All three hybrid clones secreted mAb that recognized peptide 296-322 and the recombinant protein P501N.

For FACS analysis, HEK293 cells were transiently transfected with a P501S/VR1012 expression constructs using Fugene 6 reagent. After 2 days of culture, cells were harvested and washed, then incubated with purified 4G5 mAb for 30 minutes on ice. After several washes in PBS, 0.5% BSA, 0.01% azide, goat anti-mouse Ig-FITC was added to the cells and incubated for 30 minutes on ice. Cells were washed and resuspended in wash buffer including 1% propidium iodide and subjected to FACS analysis. The FACS analysis confirmed that amino acids 296-322 of P501S are in an extracellular domain and are cell surface expressed.

The chromosomal location of P501S was determined using the GeneBridge 4 Radiation Hybrid panel (Research Genetics). The PCR primers of SEQ ID NO: 528 and 529 were employed in PCR with DNA pools from the hybrid panel according to the manufacturer's directions. After 38 cycles of amplification, the reaction products were separated on a 1.2% agarose gel, and the results were analyzed through the Whitehead Institute/MIT Center for Genome Research web server

(<http://www-genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl>) to determine the probable chromosomal location. Using this approach, P501S was mapped to the long arm of chromosome 1 at WI-9641 between q32 and q42. This region of chromosome 1 has been linked to prostate cancer susceptibility in hereditary prostate cancer (Smith *et al.* *Science* 274:1371-1374, 1996 and Berthon *et al.* *Am. J. Hum. Genet.* 62:1416-1424, 1998). These results suggest that P501S may play a role in prostate cancer malignancy.

## EXAMPLE 20

### REGULATION OF EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

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Steroid (androgen) hormone modulation is a common treatment modality in prostate cancer. The expression of a number of prostate tissue-specific antigens have previously been demonstrated to respond to androgen. The responsiveness of the prostate-specific antigen P501S to androgen treatment was examined in a tissue culture system as follows.

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Cells from the prostate tumor cell line LNCaP were plated at  $1.5 \times 10^6$  cells/T75 flask (for RNA isolation) or  $3 \times 10^5$  cells/well of a 6-well plate (for FACS analysis) and grown overnight in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum (BRL Life Technologies, Gaithersburg, MD). Cell culture was continued for an additional 72 hours in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum, with 1 nM of the synthetic androgen Methyltrienolone (R1881; New England Nuclear) added at various time points. Cells were then harvested for RNA isolation and FACS analysis at 0, 1, 2, 4, 8, 16, 24, 28 and 72-hours post androgen addition. FACS analysis was performed using the anti-P501S antibody 10E3-G4-D3 and permeabilized cells.

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For Northern analysis, 5-10 micrograms of total RNA was run on a formaldehyde denaturing gel, transferred to Hybond-N nylon membrane (Amersham Pharmacia Biotech, Piscataway, NJ), cross-linked and stained with methylene blue. The filter was then prehybridized with Church's Buffer (250 mM  $\text{Na}_2\text{HPO}_4$ , 70 mM  $\text{H}_3\text{PO}_4$ , 1 mM EDTA, 1% SDS, 1% BSA in pH 7.2) at 65 °C for 1 hour. P501S DNA was

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labeled with  $^{32}\text{P}$  using High Prime random-primed DNA labeling kit (Boehringer Mannheim). Unincorporated label was removed using MicroSpin S300-HR columns (Amersham Pharmacia Biotech). The RNA filter was then hybridized with fresh Church's Buffer containing labeled cDNA overnight, washed with 1X SCP (0.1 M NaCl, 0.03 M  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 0.001 M  $\text{Na}_2\text{EDTA}$ ), 1% sarkosyl (n-lauroylsarcosine) and exposed to X-ray film.

Using both FACS and Northern analysis, P501S message and protein levels were found to increase in response to androgen treatment.

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## EXAMPLE 20

### PREPARATION OF FUSION PROTEINS OF PROSTATE-SPECIFIC ANTIGENS

The example describes the preparation of a fusion protein of the prostate-specific antigen P703P and a truncated form of the known prostate antigen PSA. The truncated form of PSA has a 21 amino acid deletion around the active serine site. The expression construct for the fusion protein also has a restriction site at 3' end, immediately prior to the termination codon, to aid in adding cDNA for additional antigens.

The full-length cDNA for PSA was obtained by RT-PCR from a pool of RNA from human prostate tumor tissues using the primers of SEQ ID NO: 607 and 608, and cloned in the vector pCR-Blunt II-TOPO. The resulting cDNA was employed as a template to make two different fragments of PSA by PCR with two sets of primers (SEQ ID NO: 609 and 610; and SEQ ID NO: 611 and 612). The PCR products having the expected size were used as templates to make truncated forms of PSA by PCR with the primers of SEQ ID NO: 611 and 613, which generated PSA (delta 208-218 in amino acids). The cDNA for the mature form of P703P with a 6X histidine tag at the 5' end, was prepared by PCR with P703P and the primers of SEQ ID NO: 614 and 615. The cDNA for the fusion of P703P with the truncated form of PSA (referred to as FOPP) was then obtained by PCR using the modified P703P cDNA and the truncated form of PSA cDNA as templates and the primers of SEQ ID NO: 614 and 615. The FOPP



cDNA was cloned into the NdeI site and XhoI site of the expression vector pCRX1, and confirmed by DNA sequencing. The determined cDNA sequence for the fusion construct FOPP is provided in SEQ ID NO: 616, with the amino acid sequence being provided in SEQ ID NO: 617.

5                   The fusion FOPP was expressed as a single recombinant protein in *E. coli* as follows. The expression plasmid pCRX1FOPP was transformed into the *E. coli* strain BL21-CodonPlus RIL. The transformant was shown to express FOPP protein upon induction with 1 mM IPTG. The culture of the corresponding expression clone was inoculated into 25 ml LB broth containing 50 ug/ml kanamycin and 34 ug/ml  
10 chloramphenicol, grown at 37 °C to OD600 of about 1, and stored at 4 °C overnight. The culture was diluted into 1 liter of TB LB containing 50 ug/ml kanamycin and 34 ug/ml chloramphenicol, and grown at 37 °C to OD600 of 0.4. IPTG was added to a final concentration of 1 mM, and the culture was incubated at 30 °C for 3 hours. The cells were pelleted by centrifugation at 5,000 RPM for 8 min. To purify the protein, the  
15 cell pellet was suspended in 25 ml of 10 mM Tris-Cl pH 8.0, 2mM PMSF, complete protease inhibitor and 15 ug lysozyme. The cells were lysed at 4 °C for 30 minutes, sonicated several times and the lysate centrifuged for 30 minutes at 10,000 x g. The precipitate, which contained the inclusion body, was washed twice with 10 mM Tris-Cl pH 8.0 and 1% CHAPS. The inclusion body was dissolved in 40 ml of 10 mM Tris-Cl  
20 pH 8.0, 100 mM sodium phosphate and 8 M urea. The solution was bound to 8 ml Ni-NTA (Qiagen) for one hour at room temperature. The mixture was poured into a 25 ml column and washed with 50 ml of 10 mM Tris-Cl pH 6.3, 100 mM sodium phosphate, 0.5% DOC and 8M urea. The bound protein was eluted with 350 mM imidazole, 10 mM Tris-Cl pH 8.0, 100 mM sodium phosphate and 8 M urea. The fractions containing  
25 FOPP proteins were combined and dialyzed extensively against 10 mM Tris-Cl pH 4.6, aliquoted and stored at - 70 °C.

## EXAMPLE 21

REAL-TIME PCR CHARACTERIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S IN  
PERIPHERAL BLOOD OF PROSTATE CANCER PATIENTS

5           Circulating epithelial cells were isolated from fresh blood of normal individuals and metastatic prostate cancer patients, mRNA isolated and cDNA prepared using real-time PCR procedures. Real-time PCR was performed with the Taqman<sup>TM</sup> procedure using both gene specific primers and probes to determine the levels of gene expression.

10           Epithelial cells were enriched from blood samples using an immunomagnetic bead separation method (Dynal A.S., Oslo, Norway). Isolated cells were lysed and the magnetic beads removed. The lysate was then processed for poly A+ mRNA isolation using magnetic beads coated with Oligo(dT)25. After washing the beads in buffer, bead/poly A+ RNA samples were suspended in 10 mM Tris HCl pH 8.0  
15           and subjected to reversed transcription. The resulting cDNA was subjected to real-time PCR using gene specific primers. Beta-actin content was also determined and used for normalization. Samples with P501S copies greater than the mean of the normal samples + 3 standard deviations were considered positive. Real time PCR on blood samples was performed using the Taqman<sup>TM</sup> procedure but extending to 50 cycles using  
20           forward and reverse primers and probes specific for P501S. Of the eight samples tested, 6 were positive for P501S and  $\beta$ -actin signal. The remaining 2 samples had no detectable  $\beta$ -actin or P501S. No P501S signal was observed in the four normal blood samples tested.

## EXAMPLE 22

EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGENS P703P AND P501S IN  
SCID MOUSE-PASSAGED PROSTATE TUMORS

25           When considering the effectiveness of antigens in the treatment of  
30           prostate cancer, the continued presence of the antigens in tumors during androgen

ablation therapy is important. The presence of the prostate-specific antigens P703P and P501S in prostate tumor samples grown in SCID mice in the presence of testosterone was evaluated as follows.

Two prostate tumors that had metastasized to the bone were removed from patients, implanted into SCID mice and grown in the presence of testosterone. Tumors were evaluated for mRNA expression of P703P, P501S and PSA using quantitative real time PCR with the SYBR green assay method. Expression of P703P and P501S in a prostate tumor was used as a positive control and the absence in normal intestine and normal heart as negative controls. In both cases, the specific mRNA was present in late passage tumors. Since the bone metastases were grown in the presence of testosterone, this implies that the presence of these genes would not be lost during androgen ablation therapy.

#### EXAMPLE 23

##### ANTI-P503S MONOCLONAL ANTIBODY INHIBITS TUMOR GROWTH *IN VIVO*

The ability of the anti-P503S monoclonal antibody 20D4 to suppress tumor formation in mice was examined as follows.

Ten SCID mice were injected subcutaneously with HEK293 cells that expressed P503S. Five mice received 150 micrograms of 20D4 intravenously at day 0 (time of tumor cell injection), day 5 and day 9. Tumor size was measured for 50 days. Of the five animals that received no 20D4, three formed detectable tumors after about 2 weeks which continued to enlarge throughout the study. In contrast, none of the five mice that received 20D4 formed tumors. These results demonstrate that the anti-P503S Mab 20D4 displays potent anti-tumor activity *in vivo*.

#### EXAMPLE 24

##### CHARACTERIZATION OF A T CELL RECEPTOR CLONE FROM A P501S-SPECIFIC T CELL CLONE

T cells have a limited lifespan. However, cloning of T cell receptor (TCR) chains and subsequent transfer essentially enables infinite propagation of the T

cell specificity. Cloning of tumor-antigen TCR chains allows the transfer of the specificity into T cells isolated from patients that share the TCR MHC-restricting allele. Such T cells could then be expanded and used in adoptive transfer settings to introduce the tumor antigen specificity into patients carrying tumors that express the antigen. T cell receptor alpha and beta chains from a CD8 T cell clone specific for the prostate-specific antigen P501S were isolated and sequenced as follows.

Total mRNA from  $2 \times 10^6$  cells from CTL clone 4E5 (described above in Example 12) was isolated using Trizol reagent and cDNA was synthesized. To determine Va and Vb sequences in this clone, a panel of Va and Vb subtype-specific primers was synthesized and used in RT-PCR reactions with cDNA generated from each of the clones. The RT-PCR reactions demonstrated that each of the clones expressed a common Vb sequence that corresponded to the Vb7 subfamily. Furthermore, using cDNA generated from the clone, the Va sequence expressed was determined to be Va6. To clone the full TCR alpha and beta chains from clone 4E5, primers were designed that spanned the initiator and terminator-coding TCR nucleotides. The primers were as follows: TCR Valpha-6 5'(sense): GGATCC---GCCGCCACC---ATGTCACCTTTCTAGCCTGCT (SEQ ID NO: 756) BamHI site Kozak TCR alpha sequence TCR alpha 3' (antisense): GTCGAC---TCAGCTGGACCACAGCCGCAG (SEQ ID NO: 757) SalI site TCR alpha constant sequence TCR Vbeta-7. 5'(sense): GGATCC---GCCGCCACC---ATGGGCTGCAGGCTGCTCT (SEQ ID NO: 758) BamHI site Kozak TCR alpha sequence TCR beta 3' (antisense): GTCGAC---TCAGAAATCCTTTCTCTTGAC (SEQ ID NO: 759) SalI site TCR beta constant sequence. Standard 35 cycle RT-PCR reactions were established using cDNA synthesized from the CTL clone and the above primers, employing the proofreading thermostable polymerase PWO (Roche, Nutley, NJ).

The resultant specific bands (approx. 850 bp for alpha and approx. 950 for beta) were ligated into the PCR blunt vector (Invitrogen) and transformed into *E. coli*. *E. coli* transformed with plasmids containing full-length alpha and beta chains were identified, and large scale preparations of the corresponding plasmids were generated. Plasmids containing full-length TCR alpha and beta chains were submitted

for sequencing. The sequencing reactions demonstrated the cloning of full-length TCR alpha and beta chains with the determined cDNA sequences for the Vb and Va chains being shown in SEQ ID NO: 760 and 761, respectively. The corresponding amino acid sequences are shown in SEQ ID NO: 762 and 763, respectively. The Va sequence was  
5 shown by nucleotide sequence alignment to be 99% identical (347/348) to Va6.2, and the Vb to be 99% identical to Vb7 (336/338),

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration,  
10 various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS

## What is Claimed:

1. An isolated polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788 under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-

375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

(g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(b) sequences having at least 70% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(c) sequences having at least 90% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-

629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

- (d) sequences encoded by a polynucleotide of claim 1;
- (e) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and
- (f) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one polypeptide according to claim 2.



8. The fusion protein of claim 7, wherein the fusion protein comprises a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 682, 692, 695, 699, 703 and 709; and

(b) sequences encoded by SEQ ID NO: 679, 691, 696, 700, 704 and 708.

9. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 or 786-788 under moderately stringent conditions.

10. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides according to claim 2;  
(b) polynucleotides according to claim 1; and  
(c) antigen-presenting cells that express a polypeptide according to claim 1,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

11. An isolated T cell population, comprising T cells prepared according to the method of claim 10.

12. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:

- (a) polypeptides according to claim 2;
- (b) polynucleotides according to claim 1;
- (c) antibodies according to claim 5;
- (d) fusion proteins according to claim 7;
- (e) T cell populations according to claim 11; and
- (f) antigen presenting cells that express a polypeptide according to claim 2.

13. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 12.

14. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 12.

15. A method for determining the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide according to claim 9;
- (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

16. A diagnostic kit comprising at least one oligonucleotide according to claim 9.

17. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

18. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

- (a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) polypeptides according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a polypeptide of claim 2, such that T cell proliferate; and
- (b) administering to the patient an effective amount of the proliferated T cells,

thereby inhibiting the development of a cancer in the patient.

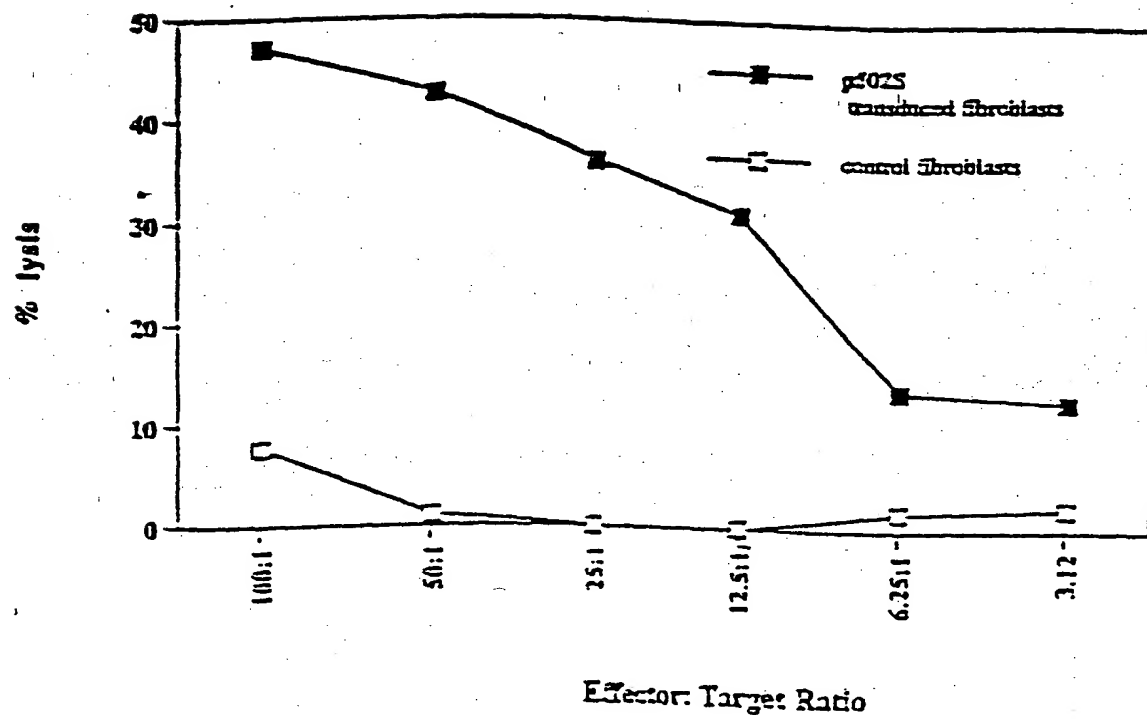


Fig. 1

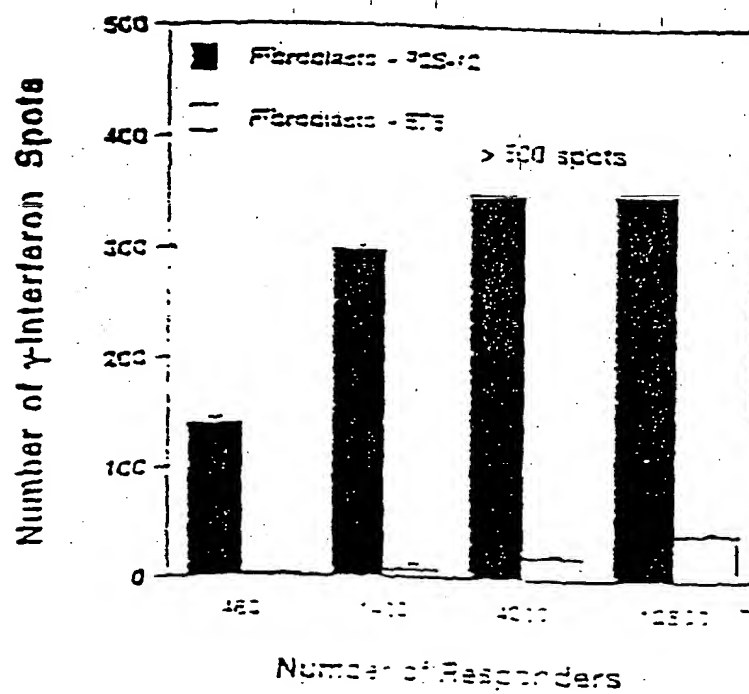


Fig. 2A

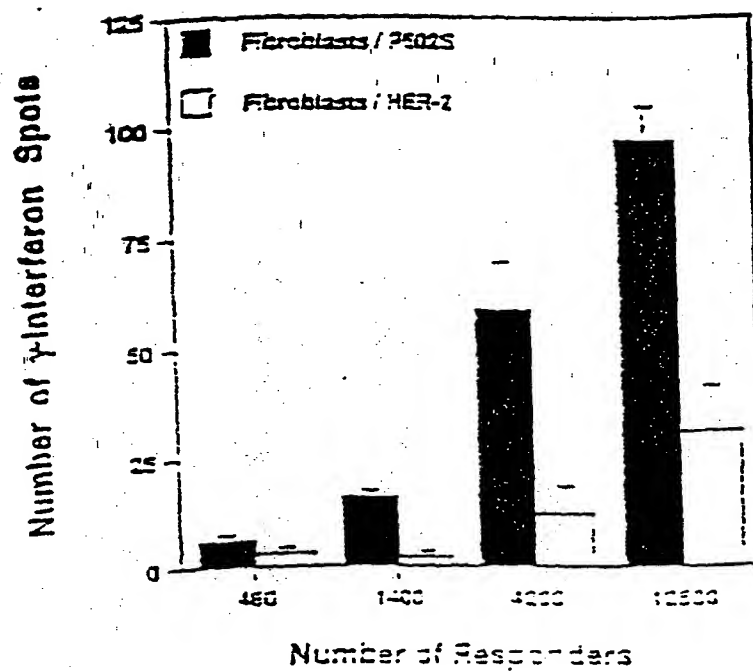


Fig. 25

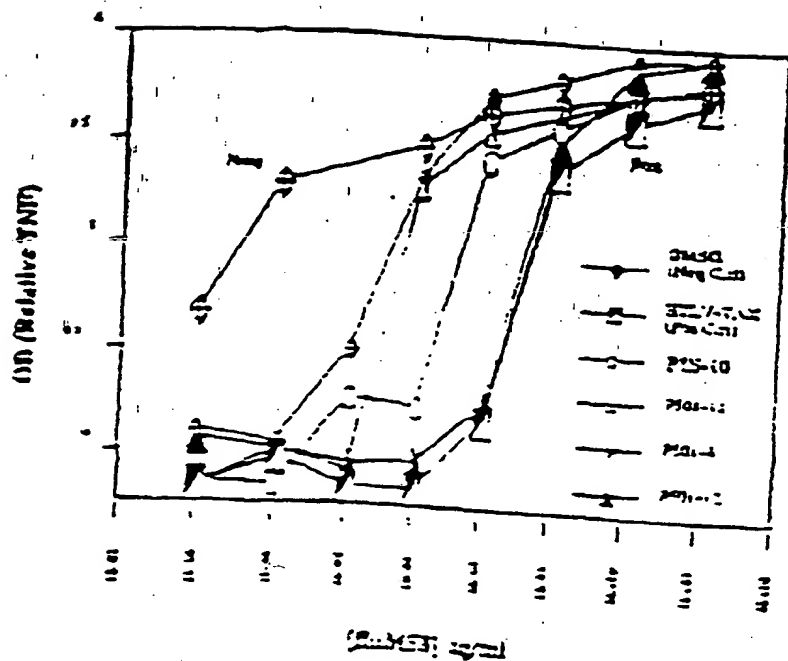


Fig. 3

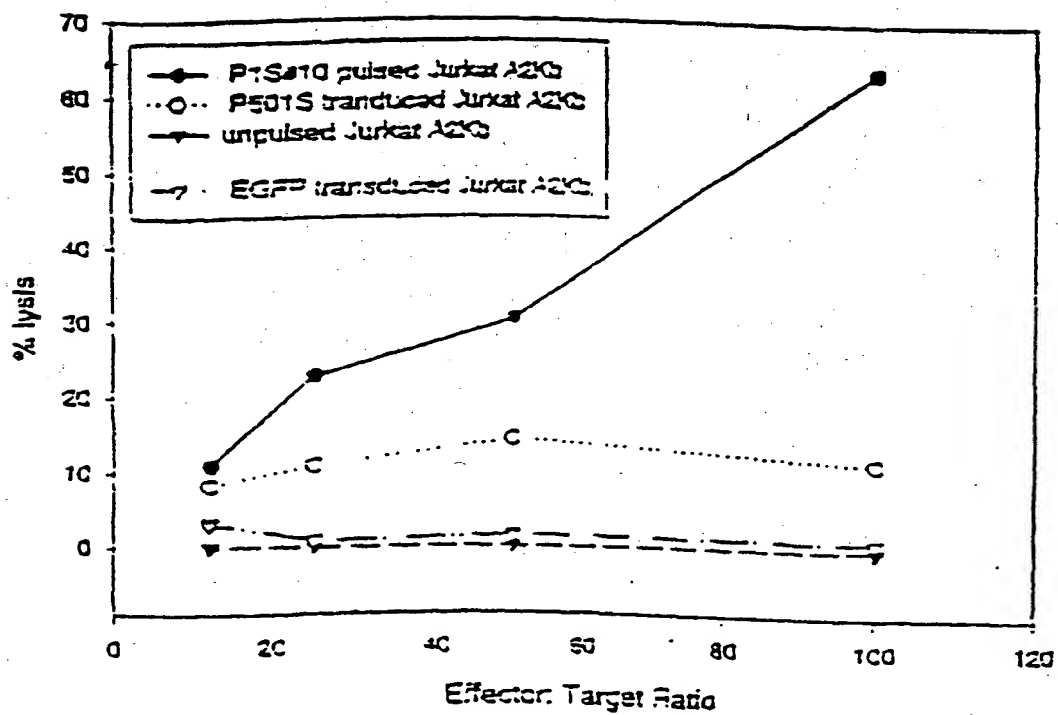


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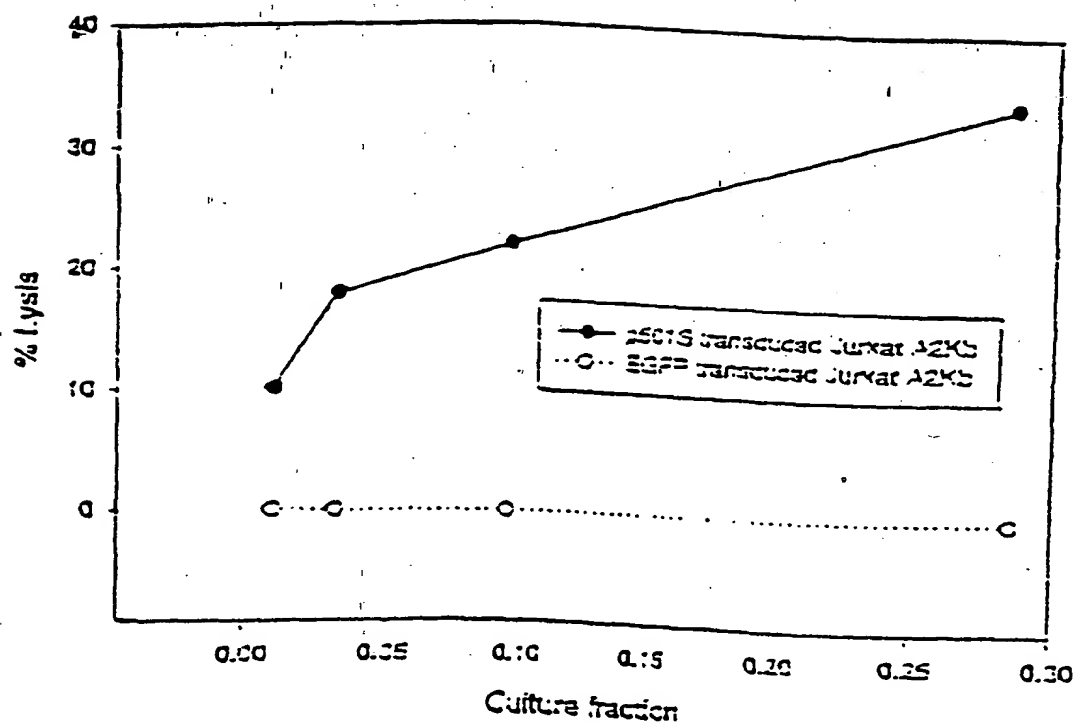


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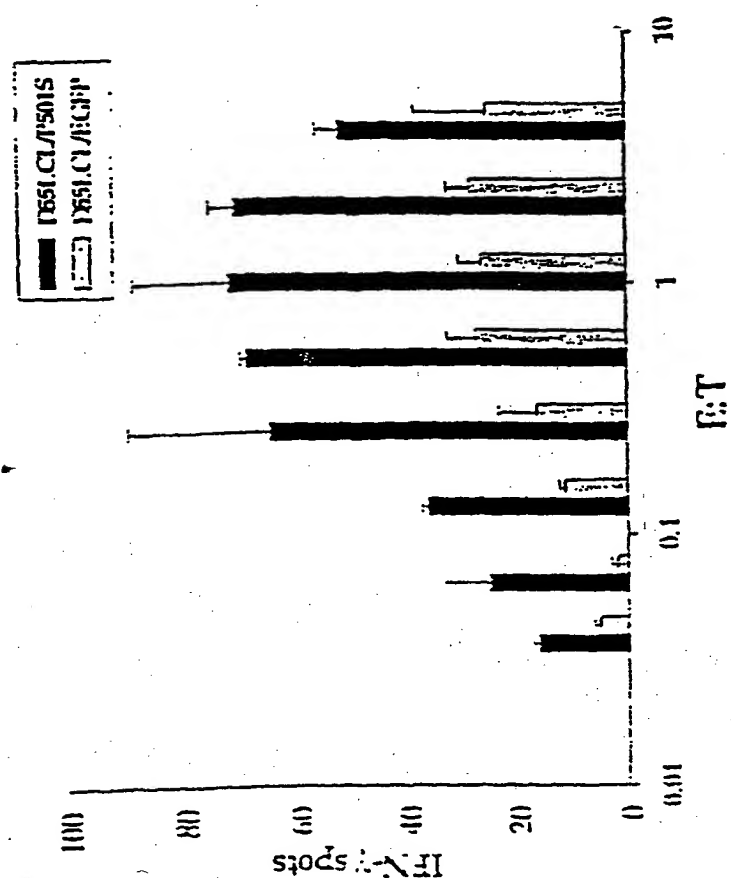


Fig. 6B

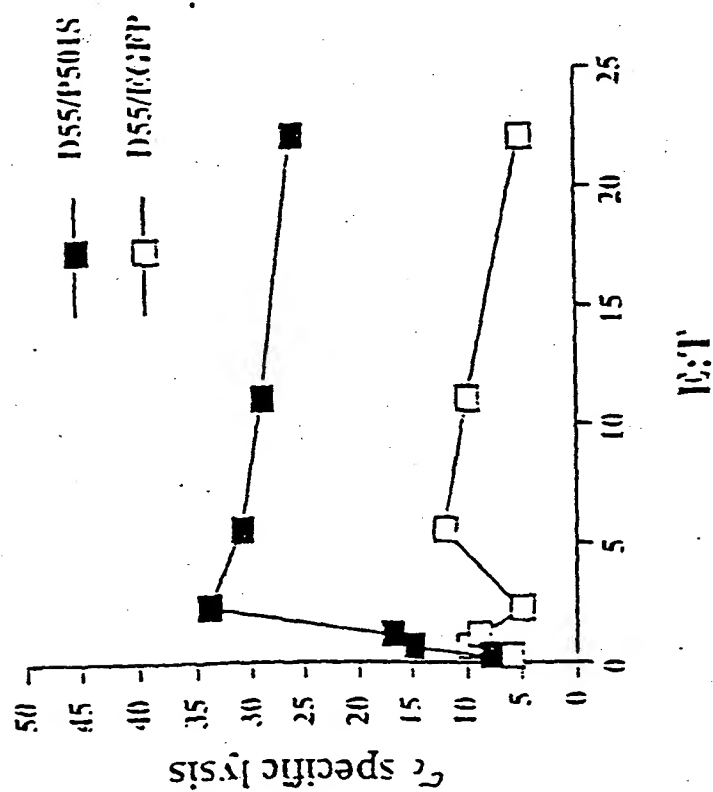
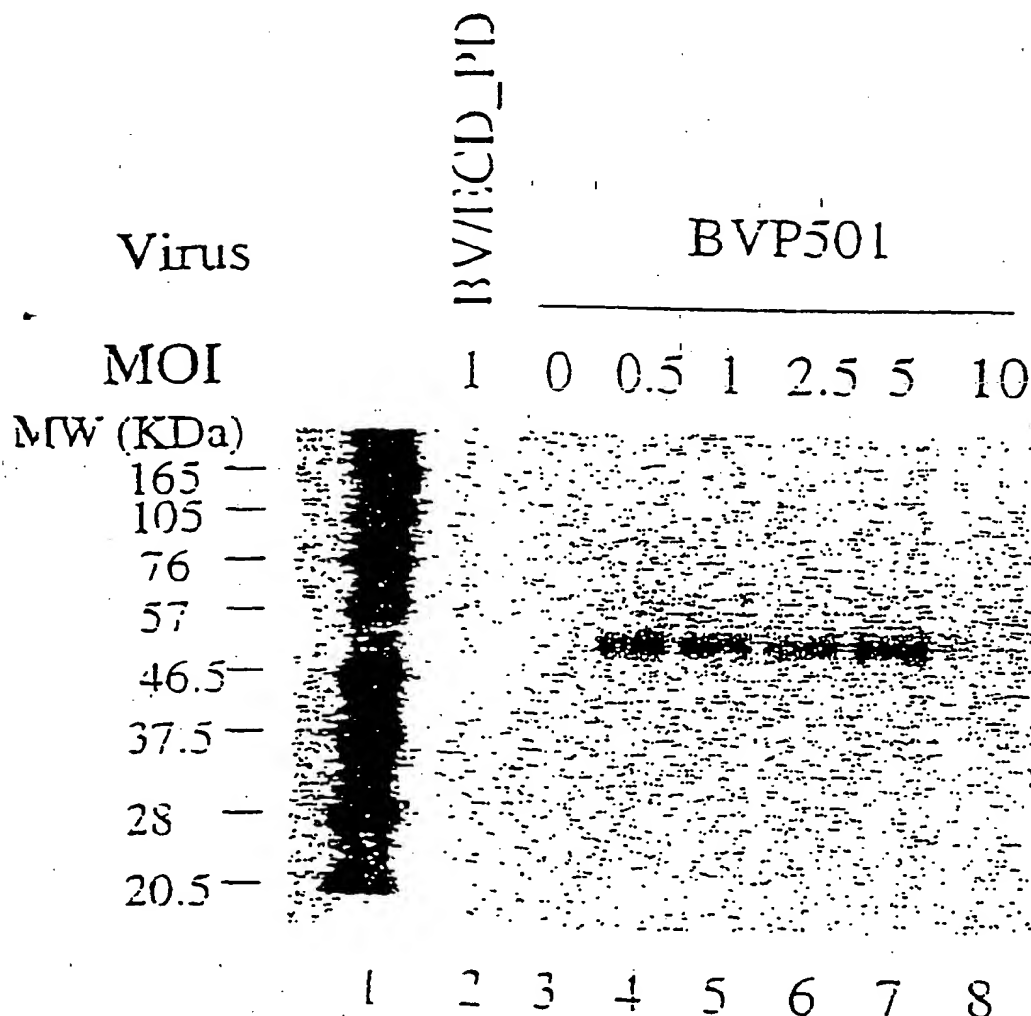


Fig. 6A

# Expression of P501S by the Baculovirus Expression System



0.6 million high 5 cells in 6-well plate were infected with an unrelated control virus BV/ECD\_PD (lane 2), without virus (lane 3), or with recombinant baculovirus for P501S at different MOIs (lane 4-8). Cell lysates were run on SDS-PAGE under the reducing conditions and analyzed by Western blot with a monoclonal antibody against P501S (P501S-10E3-G4D3). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

Fig. 7



# Figure 1. Schematic of P501S with predicted transmembrane, cytoplasmic, and extracellular regions

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Underlined sequence: Predicted transmembrane domain; **Bold sequence**: Predicted extracellular domain;

*Italic sequence*: Predicted intracellular domain. Sequence in bold/underlined: used to generate polyclonal rabbit serum

Localization of domains predicted using IMMTOPI (C.E. Tusnady and I. Simon (1998) Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to topology Prediction. J.Mol Biol. 283, 489-506.

# Genomic Map of (5) Corixa Candidate Genes

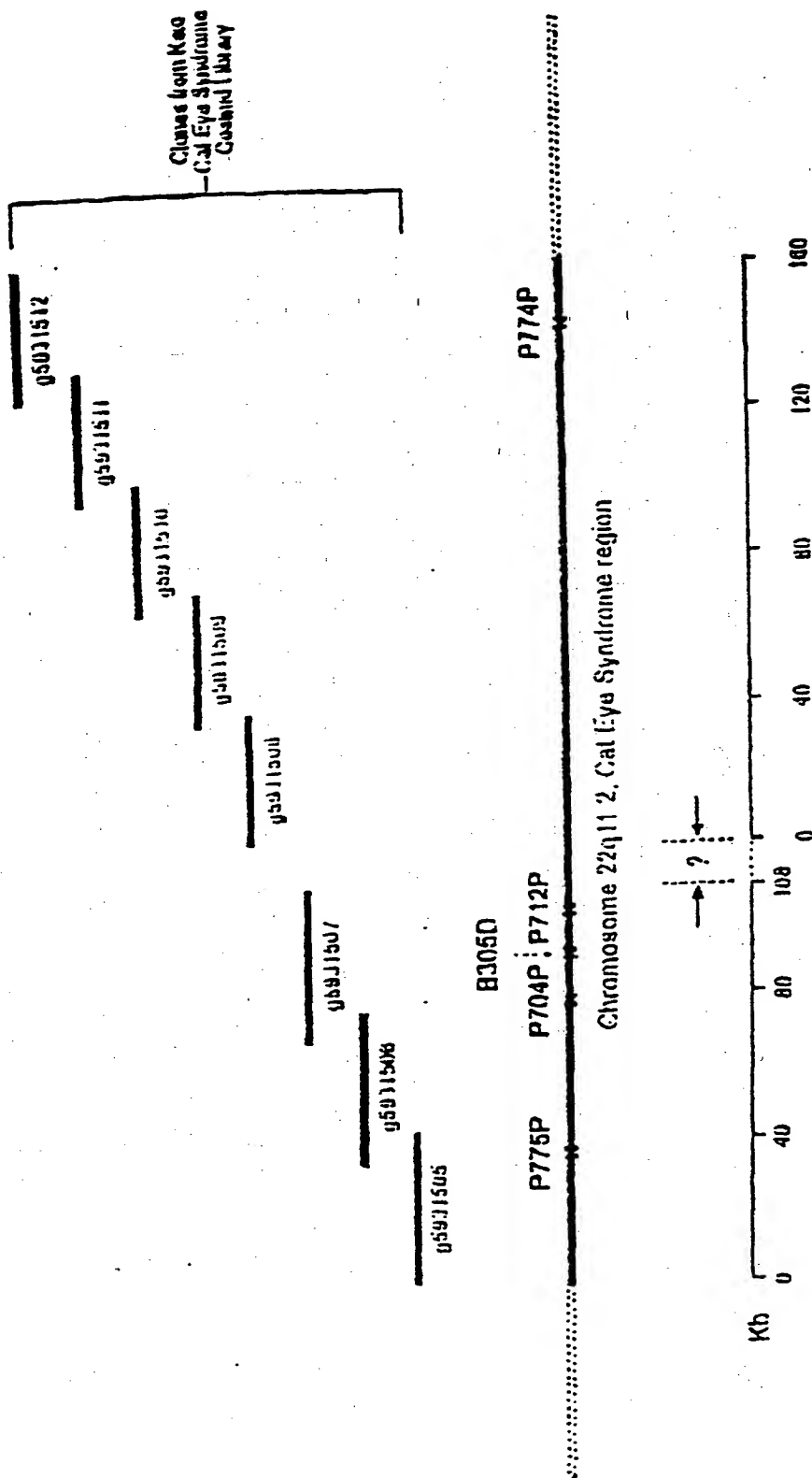


Fig. 10

# FIGURE 4. Elisa assay of rabbit polyclonal antibody specificity

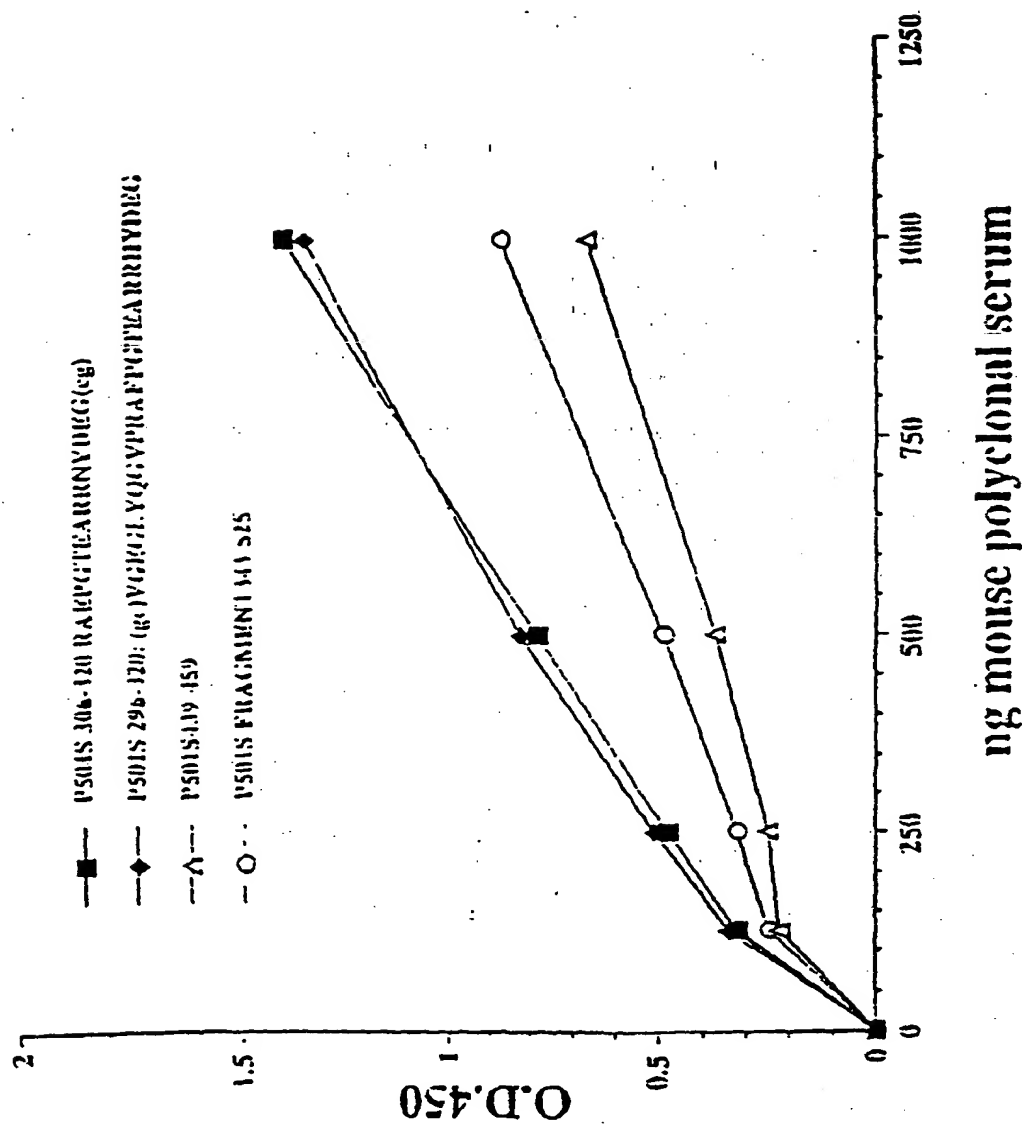


Fig. 11

## SEQUENCE LISTING

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 Smithkline Beechan Biologicals S.A.  
 Xu, Jiangchun  
 Dillon, Davin C.  
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 Harlocker, Susan L.  
 Jiang, Yuqi  
 Reed, Steven G.  
 Kalos, Michael D.  
 Fanger, Gary R.  
 Retter, Marc W.  
 Stolk, John A.  
 Day, Craig H.  
 Skeiky, Yasir A.W.  
 Wang, Aijun  
 Meagher, Medeleine Joy  
 Vanderbrugge, Didier  
 Dewerchin, Marianne  
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&lt;210&gt; 9

&lt;211&gt; 801

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(801)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 9

acgccttgat	cctcccaggc	tgggactggt	tctgggagga	gccgggcatg	ctgtggtttg	60
taangatgac	actcccaaag	gtggtcctga	cagtggccca	gatggacatg	gggtcacct	120
caaggacaag	gccaccaggt	gcgggggccc	aagcccat	gatccttact	ctatgagcaa	180
aatcccctgt	gggggcttct	ccttgaagtc	cgccancagg	gctcagtctt	tggaaccang	240
caggtcatgg	ggttgtnnc	caactggggg	ccncaacgca	aaanggcna	gggcctcngn	300
cacccatccc	angacgggc	tacactnctg	gacctccnc	tccaccactt	tcatgcgtg	360
ttcntacccg	cgatntgtc	ccanctgttt	cngtgcnc	tccancttct	nggacgtgog	420
ctacatacgc	ccggantcnc	ntcccgctt	tgccctatc	cacgtncan	caacaaattt	480
cncctantg	caccnattcc	cacnttttnc	agntttccnc	nncngcttc	cttntaaag	540
ggttganc	cggaatnnc	cccaaagggg	gggggcccng	taccaactn	ccccctnata	600
gctgaantcc	ccatnaccnn	gnctcnatgg	ancntccnt	tttaannacn	ttctnaactt	660
gggaananc	ctcgnccntn	ccccnttaa	tccnccctg	cnangnnent	cccccnntcc	720
ncccnntng	gcntntnann	cnaaaaaggc	ccnnnancaa	tctcctnnn	cctcanttgc	780
ccanccctcg	aaatcgccn	c				801

&lt;210&gt; 10

&lt;211&gt; 789

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(789)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 10

cagtctatnt	ggccagtgtg	gcagctttcc	ctgtggctgc	cggtgccaca	tgctgtccc	60
acagtgtggc	cgtggtgaca	gcttcagccg	ccctcaccgg	gttcaccttc	tcagccctgc	120
agatcctgcc	ctacacactg	gcctccctct	accaccggga	gaagcagggt	ttcctgccca	180
aataccgagg	ggacactgga	ggtgctagca	gtgaggacag	cctgatgacc	agcttccctgc	240
caggccctaa	gcctggagct	cccttcccta	atggacacgt	gggtgctgga	ggcagtggcc	300
tgctccacc	tccaccgcg	ctctgcgggg	cctctgcctg	tgatgtctcc	gtacgtgtgg	360
tggtgggtga	gcccaccgan	gccagggtgg	ttccggggcg	ggcatctgc	ctggacctgc	420
ccatcctgga	tagtgcttcc	tgctgtccca	ngtggcccca	tccctgttta	tggtgtccat	480
tgccagctc	agccagtctg	tcactgccta	tatggtgtct	gccgcaggcc	tggtgtcgtg	540
ccatttact	ttgtacaca	ggtantattt	gacaagaacg	anttgcccaa	atactcagcg	600

ttaaaaaatt	ccagcaacat	tgggggtgga	aggcctgcct	cactgggtcc	aactccccgc	660
tcctgttaac	cccatggggc	tgccggcttg	gccgccaaatt	tctgttgctg	ccaaantnat	720
gtggctctct	gtgccacct	gttgctgggt	gaagtgcnta	cngcncanct	nggggggtng	780
ggngttccc						789

<210> 11  
 <211> 772  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(772)  
 <223> n = A,T,C or G

<400> 11						
cccaccctac	ccaaatatta	gacaccaaca	cagaaaagct	agcaatggat	tcccttctac	60
tttggttaaat	aaataagtta	aatatatttaa	tgccctgtgtc	tctgtgatgg	caacagaagg	120
accaacaggc	cacatcctga	taaaaggtaa	gaggggggtg	gatcagcaaa	aagacagtgc	180
tgtgggctga	ggggacctgg	ttcttgtgtg	ttgccctca	ggactcttcc	cctacaaata	240
actttcatat	gttcaaatcc	catggaggag	tgtttcatcc	tagaaactcc	catgcaagag	300
ctacattaaa	cgaagctgca	ggtaagggg	cttanagatg	ggaaaccagg	tgactgagtt	360
tattcagctc	ccaaaaaccc	ttctctaggt	gtgtctcaac	taggaggcta	gctgttaacc	420
ctgagcctgg	gtaatccacc	tgagagctcc	ccgcattcca	gtgcatggaa	cccttctggc	480
ctccctgtat	aagtccagac	tgaaaccccc	ttggaaggnc	tccagtcagg	cagccctana	540
aactggggaa	aaaagaaaag	gacgccccan	ccccagctg	tgcanctacg	cacctcaaca	600
gcacaggggtg	gcagcaaaaa	aaccacttta	ctttggcaca	aacaaaaact	ngggggggca	660
accccggcac	cccnangggg	gttaacagga	ancngggnaa	cntggaacc	aattnaggca	720
ggccccccac	ccnnaatntt	gctgggaaat	ttttcctccc	ctaaattntt	tc	772

<210> 12  
 <211> 751  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(751)  
 <223> n = A,T,C or G

<400> 12						
gccccaatte	cagctgccac	accacccacg	gtgactgcat	tagttcggat	gtcatacaaa	60
agctgattga	agcaaccctc	tacttttttg	tcgtgagcct	tttgcttggg	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtanggtg	agtcctcaaa	atccgtatag	ttgggtgaagc	cacagcactt	gagccctttc	240
atggtggtgt	tcacacttg	agtgaagtct	tcctgggaac	cataatcttt	cttgatggca	300
ggcactacca	gcaacgtcag	ggaagtgtct	agccattgtg	gtgtacacca	aggcgaccac	360
agcagctgcn	acctcagcaa	tgaagatgan	gaggangatg	aagaagaacg	tcncgagggc	420
acacttgctc	tcagtcttan	caccatanca	gcccntgaaa	accaananca	aagaccacna	480
cncgggtgc	gatgaagaaa	tnaccccneg	ttgacaaaact	tgcatggcac	tggganccac	540
agtggccnna	aaaatcttca	aaaaggatgc	cccatcnatt	gaccccccaa	atgcccactg	600
ccaacagggg	ctgccccacn	cncnnaacga	tgancnatt	gnacaagatc	tncntggtct	660
tnatnaacnt	gaaccctgcn	tngtggctcc	tgttcaggnc	cnnngcctga	cttctnaann	720
aangaactcn	gaagncccca	cngganannc	g			751

<210> 13  
 <211> 729  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(729)

<223> n = A,T,C or G

<400> 13

gagccaggcg	tccctctgcc	tgcccactca	gtggcaacac	ccgggagctg	ttttgtcctt	60
tgtggancct	cagcagtncc	ctctttcaga	actcantgcc	aagancctg	aacaggagcc	120
accatgcagt	gcttcagctt	cattaagacc	atgatgatcc	tcttcaattt	gctcatcttt	180
ctgtgtgggtg	cagccctgtt	ggcagtgggc	atctgggtgt	caatcgatgg	ggcatccttt	240
ctgaagatct	tccggccact	gtcgtccagt	gccatgcagt	ttgtcaacgt	gggctacttc	300
ctcatcgag	ccggcggtgt	ggtcttagct	ctagggtttcc	tgggctgcta	tggtgctaag	360
actgagagca	agtgtgccct	cgtgacgttc	ttcttcatcc	tcctcctcat	cttcattgct	420
gaggttgcaa	tgtctgtggtc	gccttggtgt	acaccacaat	ggctgagcac	ttcctgacgt	480
tgtgtgtaat	gcctgccatc	aanaaaagat	tatgggttcc	caggaanact	tcaactcaagt	540
gttggaacac	caccatgaaa	gggctcaagt	gctgtggctt	cnnccaacta	tacggatttt	600
gaagantcac	ctacttcaaa	gaaaanagt	cctttccccc	atttctgttg	caattgacaa	660
acgtcccaaa	cacagccaat	tgaaaacctg	cacccaaccc	aaanggggtcc	ccaaccanaa	720
attnaagg						729

<210> 14

<211> 816

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(816)

<223> n = A,T,C or G

<400> 14

tgctcttct	caaagttggt	cttgttgcca	taacaaccac	cataggtaaa	gcgggagcag	60
tggtcgctga	aggggttgta	gtaccagcgc	gggatgctct	ccttgacagag	tcctgtgtct	120
ggcaggtcca	cgagtgccc	tttgtcactg	gggaaatgga	tgcgctggag	ctcgtcaaag	180
ccactcgtgt	atttttcaca	ggcagcctcg	tcggagcggt	cggggagctt	gggggtgtct	240
tcacactcca	ggaaactgtc	natgcagcag	ccattgctgc	agcggaactg	ggtgggctga	300
cangtgccag	agcacactgg	atggcgctt	tcctatgnan	gggccctgng	ggaaagtccc	360
tgancccan	anctgcctct	caaangcccc	accttgacac	ccccgacagg	ctagaatgga	420
atcttcttcc	cgaaaggtag	ttnttctgt	tgcccaancc	anccccntaa	acaaactctt	480
gcanatctgc	tccngggggg	tontantacc	ancgtgggaa	aagaacccca	ggcngcgaac	540
caancttggt	tggatncgaa	gcnataatct	nctnttctgc	ttggtggaca	gcaccantna	600
ctgtnnanct	ttagnccntg	gtcctcntgg	ggtgnncttg	aacctaatcn	ccnntcaact	660
gggacaaggt	aantngccnt	cctttnaatt	cccnancntn	ccccctgggt	tgggggtttt	720
cncnctcta	ccccagaaan	nccgtgttcc	cccccaacta	ggggccnaaa	ccnnttnttc	780
cacaacctn	ccccacccac	gggttcngnt	ggttng			816

<210> 15

<211> 783

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(783)

<223> n = A,T,C or G

&lt;400&gt; 15

ccaaggcctg	ggcaggcata	nacttgaagg	tacaacccca	ggaaccctg	gtgctgaagg	60
atgtggaaaa	cacagattgg	cgctactgc	ggggtgacac	ggatgtcagg	gtagagagga	120
aagacccaaa	ccaggtggaa	ctgtggggac	tcaaggaang	cacctacctg	ttccagctga	180
cagtgactag	ctcagaccac	ccagaggaca	cggccaacgt	cacagtcact	gtgctgtcca	240
ccaagcagac	agaagactac	tgcctcgcac	ccaacaangt	gggtcgctgc	cggggtctt	300
tcccacgctg	gtactatgac	cccacggagc	agatctgcaa	gagtttcgtt	tatggagggt	360
gcttgggcaa	caagaacaac	taccttcggg	aagaagagt	cattctancc	tgtcnggggt	420
tgcaaggtgg	gcctttgana	ngcanctctg	gggtcangc	gactttcccc	cagggccccct	480
ccatggaaa	gcgccatcca	ntgttctctg	gcacctgtca	gccacccag	ttccgctgca	540
ncaatggctg	ctgcatcnac	antttcctng	aattgtgaca	acaaccccca	ntgcccccaa	600
ccctcccaac	aaagcttcgc	tgttnaaaaa	tacnccantt	ggcttttnac	aaacnccogg	660
cncctcctt	ttcccnntn	aacaaagggc	nctngcctt	gaactgccn	aaccnnggaa	720
tctnccnngg	aaaaantncc	ccccctggtt	cctnnaancc	cctccncaaa	anctncccc	780
ccc						783

&lt;210&gt; 16

&lt;211&gt; 801

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(801)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 16

gccccaatc	cagctgccac	accacccacg	gtgactgcat	tagttcggat	gtcatacaaa	60
agctgattga	agcaaccctc	tacttttttg	tcgtgagcct	tttgcttggg	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtaggggtg	agtcctcaaa	atccgtatag	ttggtgaagc	cacagcactt	gagccctttc	240
atgggtgggtg	tccacacttg	agtgaagtct	tcctgggaac	cataatcttt	cttgatggca	300
ggcactacca	gcaacgtcag	gaagtgtctc	gccattgtgg	tgtacaccaa	ggcgaccaca	360
gcagctgcaa	cctcagcaat	gaagatgagg	aggaggatga	agaagaacgt	cncgagggca	420
cacttgctct	ccgtcttagc	accatagcag	cccangaaac	caagagcaaa	gaccacaacg	480
ccngctgcga	atgaaagaaa	ntaccacacg	tgacaaactg	catggccact	ggacgacagt	540
tggcccgaan	atcttcagaa	aagggatgcc	ccatcgattg	aacacccana	tgcccactgc	600
cnacagggct	gcnccnccn	gaaagaatga	gccattgaag	aaggatcctc	ntggtcttaa	660
tgaactgaaa	ccntgcatgg	tggccctgt	tcagggtctc	tggcagtga	ttctganaaa	720
aaggaacngc	ntnagcccc	ccaaangana	aaacaccccc	gggtgttgcc	ctgaattggc	780
ggccaaggan	ccctgccccn	g				801

&lt;210&gt; 17

&lt;211&gt; 740

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(740)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 17

gtgagagcca	ggcgtccctc	tgcctgcccc	ctcagtgcca	acacccggga	gctgttttgt	60
cctttgtgga	gcctcagcag	ttccctcttt	cagaactcac	tgccaagagc	cctgaacagg	120
agccaccatg	cagtgtctca	gcttcattaa	gaccatgatg	atcctcttca	atttgctcat	180
ctttctgtgt	gggtgcagccc	tgttggcagt	gggcatctgg	gtgtcaatcg	atggggcatc	240
ctttctgaag	atcttcgggc	cactgtcgtc	cagtgccatg	cagtttgtca	acgtgggcta	300

cttcctcatc	gcagccggcg	ttgtggtcct	tgctcttggt	ttcctgggct	gctatggtgc	360
taagacggag	agcaagtgtg	ccctcgtgac	gttcttcttc	atcctcctcc	tcctcttcat	420
tgctgaagtt	gcagctgctg	tggtcgcctt	ggtgtacacc	acaatggctg	aaccattcct	480
gacgttgctg	gtantgcctg	ccatcaanaa	agattatggg	ttcccaggaa	aaattcactc	540
aantntggaa	caccnccatg	aaaagggctc	caattttctgn	tggtctcccc	aactataccg	600
gaattttgaa	agantcncct	tacttccaaa	aaaaaanant	tgcttttnc	cccnttctgt	660
tgcaatgaaa	acntcccaan	acngccaatn	aaaacctgcc	cnnncaaaaa	ggntcncaaa	720
caaaaaaant	nnaagggttn					740

&lt;210&gt; 18

&lt;211&gt; 802

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(802)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 18

ccgctgggtg	cgctgggtcca	gngnagccac	gaagcacgtc	agcatcacaca	gcctcaatca	60
caaggtcttc	cagctgcgcg	acattacgca	gggcaagagc	ctccagcaac	actgcatatg	120
ggatacactt	tacttttagca	gccaggggtga	caactgagag	gtgtcgaagc	ttattcttct	180
gagcctctgt	tagtggagga	agattccggg	cttcagctaa	gtagtcagcg	tatgtcccat	240
aagcaaacac	tgtgagcagc	cgggaaggtag	aggcaaaagtc	actctcagcc	agctctctaa	300
cattgggcat	gtccagcagt	tctccaaaca	cgtagacacc	agnggcctcc	agcacctgat	360
ggatgagtgt	ggccagcgct	gcccccttgg	ccgacttggc	taggagcaga	aattgctcct	420
ggttctgccc	tgtcaccttc	acttccgcac	tcactactgc	actgagtgtg	ggggacttgg	480
gctcaggatg	tccagagacg	tggttccgcc	ccctcnctta	atgacaccgn	ccanncaacc	540
gtcggctccc	gccgantng	ttcgtcgtnc	ctgggtcagg	gtctgctggc	cnctacttgc	600
aancttcgtc	nggcccattg	aattcacenc	accggaaactn	gtangatcca	ctnnttctat	660
aaccggnccg	caccgcnnnt	ggaactccac	tcttnttnc	tttacttgag	ggttaaggtc	720
accctttnccg	ttaccttggg	ccaaaccntn	ccntgtgtcg	anatngtnaa	tcnggncna	780
tnccanccnc	atangaagcc	ng				802

&lt;210&gt; 19

&lt;211&gt; 731

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(731)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 19

cnaagcttcc	aggtnacggg	ccgcnaaanc	tgaccenagg	tancanaang	cagnncggcg	60
gagccaccg	tcacgnngng	ngtctttat	nggagggggc	ggagccacat	cnctggacnt	120
cntgaccca	actcccncc	ncncantgca	gtgatgagt	cagaactgaa	ggtnacgtgg	180
caggaacca	gancaaannc	tgctccnntc	caagtcggcn	nagggggcg	ggctggccac	240
gcncatccnt	cnagtgtgn	aaagcccn	cctgtctact	tgtttgaga	acngcnnga	300
catgcccagn	gttanataac	ngcngagag	tnantttgcc	tctcccttcc	ggetgcgan	360
cngtntgt	tagnggacat	aacctgacta	cttaactgaa	cccnngaate	tnccnccct	420
ccactaagct	cagaacaaaa	aacttcgaca	ccactcantt	gtcacctgnc	tgctcaagta	480
aagtgtaccc	catncccaat	gtntgctnga	ngctctgnc	tgcnttangt	tcggtcctgg	540
gaagacctat	caattnaagc	tatgtttctg	actgcctctt	gctccctgna	acaancnacc	600
cnncnntcca	agggggggnc	ggcccccaat	ccccccaacc	ntnaattnan	tttancccn	660
ccccnggcc	cggcctttta	cnancntcnn	nnacngggna	aaaccnnngc	tttncccaac	720



nnaatccncc t

731

&lt;210&gt; 20

&lt;211&gt; 754

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(754)

&lt;223&gt; n = A, T, C or G

&lt;400&gt; 20

tttttttttt	tttttttttt	taaaaacccc	ctccattnaa	tgnaaaacttc	cgaaattgtc	60
caaccacctc	ntccaaatnn	ccntttccgg	gnngggggttc	caaacccean	ttanntttgg	120
annttaaatt	aaatnttntt	tgngnggnna	anccnaatgt	nangaaagtt	naaccanta	180
tnancttnaa	tnectggaaa	ccngtngntt	ccaaaaatnt	ttaaccctta	antccctecg	240
aaatngttna	nggaaaaccc	aantttctnt	aaggttggtt	gaaggntnaa	tnaaaanccc	300
nnccaattgt	tttngccac	gcctgaatta	attggnttcc	gntgttttcc	nttaaaaana	360
ggnnancccc	ggttantnaa	tccccccnnc	cccaattata	ccganttttt	ttngaattgg	420
gancccnccg	gaattaacgg	ggnnntccc	tnttgggggg	cnggnncccc	ccccntcggg	480
ggttngggnc	aggnchnaat	tgtttaaggg	tccgaaaaat	ccctccnaga	aaaaaanctc	540
ccaggttgag	nntnggggtt	cccccccccc	cangggccct	ctcgnanagt	tgggggttgg	600
ggggcctggg	attttntttc	ccctnttnc	tcccccccc	ccnggganag	aggttngngt	660
tttgntcnnc	ggcccnccn	aaganctttn	ccganttnan	ttaaactcnt	gcctnggcga	720
agtccnttgn	agggntaaan	ggccccctnn	cggg			754

&lt;210&gt; 21

&lt;211&gt; 755

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(755)

&lt;223&gt; n = A, T, C or G

&lt;400&gt; 21

atcancccat	gaccccnac	nngggacnc	tcancggnc	nnncnaccnc	cgcccnatca	60
nngtagnnnc	actncnnttn	natcacnccc	cncnactac	gcccnananc	cnacgcncta	120
nncanatncc	actganngcg	cgangtngan	ngagaaanct	nataccanag	ncaccanacn	180
ccagctgtcc	nanaangcct	nnnatacnng	nnnatccaat	ntgnancctc	cnaagtattn	240
nncnncanac	gattttcctn	anccgattac	ccntncccc	tanccctcc	cccccaacna	300
cgaaggcnct	ggnccnaagg	nngcgnccc	ccgctagntc	cccncaagt	cncnnccta	360
aactcanccn	nattacncgc	ttcntgagta	tcactccccg	aatctcacc	tactcaactc	420
aaaaanctn	gatacaaaa	aatncaagcc	tgnttatnac	actntgactg	ggtctctatt	480
ttagnngtcc	ntnaancntc	ctaatacttc	cagctcncct	tonccaattt	ccnaanggct	540
ctttcngaca	gcatnttttg	gttcccnntt	gggttcttan	ngaattgccc	ttcntngaac	600
gggtctentct	tttccttcgg	ttancctggg	ttcnccggc	cagttattat	ttcccntttt	660
aaattcntnc	cntttanttt	tggcnttcna	aacccccggc	cttgaaaacg	gccccctggg	720
aaaagggttg	tttganaaaa	ttttgtttt	gttcc			755

&lt;210&gt; 22

&lt;211&gt; 849

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

<221> misc\_feature  
 <222> (1)...(849)  
 <223> n = A,T,C or G

<400> 22  
 tttttttttt ttttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt 60  
 acgctnggan taangcgacc cgantttctag ganncnccct aaaatcanac tgtgaagatn 120  
 atcctgnnna cgggaanggtc accggnngat nntgctaggg tgnccnctcc cannncttn 180  
 cataactcng nggcctgcc caccaccttc ggcgggccng ngncggggcc cgggtcattn 240  
 gnnttaaccn cactnngcna ncggtttccn nccccnnng acccnggcga tccgggggtnc 300  
 tctgtcttcc cctgnagncn anaaantggg ccnecgnccc ctttaccctt nnacaagcca 360  
 cngcenteta nccnngccc cccctccant nngggggact gccnannigt ccgttntng 420  
 nnaccccnnn gggtncctcg gttgtcgant cnaccgnang ccanggatc cnaaggaagg 480  
 tgcgttpttg gcccctaccc ttcgctnccg nncaccttc ccgacnanga nccgtcccg 540  
 cncnncgnga cctcncctcg caacaccgc nctctcngt nccggnnccc cccaccgcg 600  
 nccctcncnc ngncgnancn ctcnccncc gtctcannca ccaccccgcc ccgccaggcc 660  
 ntcanccacn ggnngacnng nagnccntc gcncgcgcn gdgncnccct cgcncngaa 720  
 ctncntcngg ccantnncgc tcaanccna cnaaacgcg ctgcgcggcc cgnagcgncc 780  
 nectcncga gtcctcccgn ctccnacc cangnttccn cgaggacacn nnaccccgcc 840  
 nncangcgg 849

<210> 23  
 <211> 872  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(872)  
 <223> n = A,T,C or G

<400> 23  
 gcgcaaaacta tacttcgctc gnaactcgtgc gcctcgctnc tcttttctc cgcaaccatg 60  
 tctgacnanc ccgattnggc ngatattcnan aagntcganc agtccaaact gantaacaca 120  
 cacacnncan aganaaatcc nctgccttcc anagtanaacn attgaacnng agaaccangc 180  
 nggcgaatcg taatnaggcg tgcgcgcgca atntgtcncc gtttatntn ccagctcnc 240  
 ctncnacc cactctctcn nagctgtcnn acccctngtn cgnacccccc naggtcggga 300  
 tcgggttttn nntgaccgng cnnccctcc cccctccat nacganccnc ccgcaccacc 360  
 nanngcncgc nccccgnct ctgcgcnc ctgtcctntn cccctgtngc ctggcncngn 420  
 accgcattga cctcgcgcn ctncnngaaa ncgnanacgt ccgggttggn annancgctg 480  
 tgggnnngcg tctgcncgc gttccttcn ncncttcca ccatcttct tacngggtct 540  
 ccncgcctc tcnnncacnc cctgggacgc tntcctntgc ccccttnac tccccctt 600  
 cgnctgncc cgncccccacc ntcatttnca nacgntcttc acaannccct ggntnntcc 660  
 cnancngnch gtcanccnag ggaagggngg ggnncnntg nttgacgttg ngngangtc 720  
 cgaanantcc tcncctcan cctaccct cgggcgnct ctngttnc aacttancaa 780  
 ntctcccccg ngngcncntc tcagcctcnc cnccccnct ctctgcantg tntctgctc 840  
 tnaccnntac gantnttcgn cncctcttt cc 872

<210> 24  
 <211> 815  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(815)  
 <223> n = A,T,C or G

<400> 24

gcatgcaagc	ttgagtattc	tatagngtca	cctaaatanc	ttggcntaat	catggctcnta	60
nctgncttcc	tgtgtcaaat	gtatacnaaa	tanatatgaa	tctnatntga	caaganngta	120
tctntcatta	gtaacaantg	tnntgtccat	cctgtcngan	canattccca	tnnattncgn	180
cgcattcncn	gcncantatn	taatngggaa	ntcnntnnnn	ncaccnncat	ctatcntncc	240
gcncctgac	tggnagagat	ggatnanttc	tnntntgacc	nacatgttca	tcttggattn	300
aananccccc	cgcngnccac	cgggtngnng	cnagccnntc	ccaagacctc	ctgtggaggt	360
aacctgcgtc	aganncatca	aacntgggaa	acccgcnncc	angtnnaagt	ngnnncanan	420
gatcccgtcc	aggnttnacc	atcccttcnc	agcgcgccct	ttngtgcctt	anagnnagc	480
gtgtccnanc	cnetcaacat	ganacgcgcc	agnccanccg	caattnggca	caatgtcgcnc	540
gaacccccc	gggggantna	tncaaanccc	caggattgtc	cncncangaa	atcccnanc	600
ccnccctac	ccncttttg	gacngtgacc	aantcccgga	gtncacgtcc	ggccngnctc	660
ccccaccggt	nnccntgggg	gggtgaanct	cngnntcanc	cngncgaggn	ntcgnaagga	720
accggnccctn	ggncgaanng	ancnntcnga	agncccnct	cgtataaccc	cccctcncca	780
nccnactngnt	agntccccc	cngggtnccg	aangg			815

&lt;210&gt; 25

&lt;211&gt; 775

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(775)

&lt;223&gt; n = A,T,C or G

<400> 25

ccgagatgtc	tcgctccgtg	gccttagctg	tgctcgcgct	actctctctt	tctggcctgg	60
aggctatcca	gcgtactcca	aagattcagg	tttactcacg	tcattccagca	gagaatggaa	120
agtcaaattt	cctgaattgc	tatgtgtctg	ggtttcatcc	atccgacatt	gaanttact	180
tactgaagaa	tgganagaga	attgaaaaag	tgagcattc	agacttgtct	ttcagcaagg	240
actggtcttt	ctatctcntg	tactacactg	aattcaccce	cactgaaaaa	gatgagtatg	300
cctgccgtgt	gaaccatgtg	actttgtcac	agcccaagat	agttaagtgg	gatcgagaca	360
tgtaagcagn	cnnatggaa	gtttgaagat	gccgcatttg	gattggatga	attccaaatt	420
ctgcttgctt	gcnttttaat	antgatatgc	ntatacacc	taccctttat	gnccccaat	480
tgtaggggtt	acatnantgt	tcnctntngg	catgatcttc	ctttataant	ccnccnttcg	540
aattgccgtg	cncnctgtt	ngaattgttc	cnnaaccacg	gttggtctcc	ccaggtcncc	600
tcttacggaa	gggcctgggc	cncctttnca	gggtggggga	accnaaaatt	tcncttntgc	660
ccncccncca	cnntcttgng	nnncantttt	ggaacccttc	cnattccctt	tggcctcnna	720
nccttnncta	anaaaacttn	aaancgtngc	naaanntttt	acttcccccc	ttacc	775

&lt;210&gt; 26

&lt;211&gt; 820

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(820)

&lt;223&gt; n = A,T,C or G

<400> 26

anattantac	agtgtaatct	tttcccagag	gtgtgtanag	ggaacggggc	ctagaggcat	60
cccanagata	ncttatanca	acagtgcctt	gaccaagagc	tgctgggcac	atttcctgca	120
gaaaagggtg	cgtccccat	cactctctct	ctcccatagc	catcccagag	gggtgagtag	180
ccatcangcc	ttcggtggga	gggagtcang	gaaacaacan	accacagagc	anacagacca	240
ntgatgacca	tgggcggggg	cgagcctctt	ccctgnaccg	gggtggcana	nganagccta	300
nctgaggggt	cacactataa	acgttaacga	ccnagatnan	cacctgcttc	aagtgcaccc	360

ttcctacctg	acnaccagng	accnnnaact	gngcctggg	gacagcncctg	ggancagcta	420
acnnagcaact	cacctgcccc	cccatggccg	tnccgntccc	tggtcctgnc	aagggaagct	480
ccctgttgga	attncgggga	naccaaggga	nccccctcct	ccanctgtga	aggaaaaann	540
gatggaattt	tncccttccg	gccnntcccc	tcttccttta	cacgccccct	ntactcctc	600
tcctctnttt	ntcctgncnc	acttttnacc	ccnnnatttc	ccttnattga	tcggannctn	660
ganattccac	tnnccgctnc	cntcnatcng	naanacnaaa	nactntctna	cccnggggat	720
gggnncctcg	ntcatcctct	ctttttcnc	accnccnntt	ctttgcctct	ccttngatca	780
tcacaacntc	gntggccntn	ccccccnnn	tcctttnc			820

&lt;210&gt; 27

&lt;211&gt; 818

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(818)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 27

tctgggtgat	ggcctcttcc	tcctcaggga	cctctgactg	ctctgggcca	aagaatctct	60
tggtttcttct	ccgagcccca	ggcagcggtg	attcagccct	gcccacactg	attctgatga	120
ctgcggatgc	tgtgacggac	ccaaggggca	aatagggtcc	cagggtccag	ggagggggcg	180
ctgctgagca	cttcgcgcc	tcacctgcc	cagccctgc	catgagctct	gggctgggtc	240
tcgcctcca	gggttctgct	cttcangca	ngccancaa	tggcgctggg	ccacactggc	300
ttcttctg	ccntccctg	gctctgantc	tctgtcttcc	tgctctgtgc	angcnccttg	360
gatctcagtt	tcctctnctc	anngaactct	gtttctgann	tcttcantta	actntgantt	420
tatnaccnan	tggnctgtnc	tgtcnnactt	taatgggccc	gaccggctaa	tcctccctc	480
ntcccttcc	anttcnnna	accngcttnc	cntctctcc	ccntancecg	ccnggggaanc	540
ctcctttgcc	ctnaccangg	gccnnnaccg	ccctnnctn	ggggggcng	gtnnctnenc	600
ctgntnnccc	cntcncnnt	tnccctgtcc	cnnccnccn	nngcannntc	ncngtcccn	660
tnnctcttcn	ngntcgnaa	ngntcncntn	tnnnnngn	ngntnntn	tcctctcnc	720
cnnntgnang	tnnttnnnnc	ncngncccc	nnnnnnnnn	nggnntnnn	tctnccngc	780
ccnncccc	ngnattaagg	cctccnntct	ccggccnc			818

&lt;210&gt; 28

&lt;211&gt; 731

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(731)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 28

aggaagggcg	gagggatatt	gtangggatt	gagggatagg	agnataangg	gggaggtgtg	60
tcccaacatg	anggtgngt	tctcttttga	angaggggtg	ngtttttann	ccnggtgggt	120
gattnaaccc	cattgtatgg	agnnaaagg	tttnagggat	ttttcggtc	ttatcagtat	180
ntanattcct	gtnaatcgga	aatnatntt	tcnnccggaa	aatnttgctc	ccatccgnaa	240
attntcccg	ggtagtgc	nttngggggn	cngccangtt	tcccaggctg	ctanaatcgt	300
actaaagntt	naagtgggan	tncaaatgaa	aacctnnac	agagnatccn	tacccgactg	360
tnnnttnect	tcgcctntg	actctgcng	agcccaatac	ccnngngnat	gtcncnccng	420
nnngcgnenc	tgaaannnn	tcngggctnn	gancatcang	gggtttcgca	tcaaaagcnn	480
cgtttcncat	naaggcactt	tnccctcatc	caacnctng	ccctcnncca	tttngccgtc	540
nggttcnct	acgctnntng	cncctnnntn	ganattttnc	ccgcctnggg	naancctcct	600
gnaatgggta	gggncctntc	ttttnacn	ngggntnact	aatcnnctnc	acgctnctt	660
tctcnacccc	ccccctttt	caatccccanc	ggcnaatggg	gtctccccnn	cgangggggg	720

nnncccannc c

731

<210> 29  
 <211> 822  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1) ... (822)  
 <223> n = A, T, C or G

<400> 29  
 actagtccag tgtgggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat 60  
 cgctcanacc tcacancctc ccnacnange ctataangaa nannaataga nctgtncnnt 120  
 atntntacnc tcatannctt cnnnaccac tccctcttaa cccntactgt gcctatngcn 180  
 tnntantct ntgcgcgctn cnanccacn gtggggcnac cncnngnatt ctcnatctcc 240  
 tcnccatntn gcctananta ngtncatacc ctatacctac nccaatgcta nnnctaancn 300  
 tccatnantt annntaacta ccactgacnt ngactttnc atnancctct aatttgaatc 360  
 tactctgact cccacngcct annnattagc anontcccc nachatntct caaccaaadc 420  
 ntcaacaacc tatctantct ttcnccaaac nttnoctccg atccccnnac aacccccctc 480  
 ccaaataccc nccacctgac ncctaaccn caccatcccg gcaagccnan ggnccatttan 540  
 ccaactggaat cacnatngga naaaaaaac ccnaactctc tancncnnat ctccctaana 600  
 aatnctcctn naatttactn ncantnccat caanccacn tgaaacnnaa cccctgtttt 660  
 tanatccctt ctttcgaaaa ccnacccttt annncccaac ctttngggcc ccccnctnc 720  
 ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaaggcna anannntccg 780  
 canatcctat cccttanttn ggggnccctt nccnngggcc cc 822

<210> 30  
 <211> 787  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1) ... (787)  
 <223> n = A, T, C or G

<400> 30  
 cggccgcctg ctctggcaca tgcctcctga atggcatcaa aagtgatgga ctgcccattg 60  
 ctagagaaga cttctctctc tactgtcatt atggagccct gcagactgag ggctcccctt 120  
 gtctgcagga tttgatgtct gaagtctgtg agtgtggctt ggagctcctc atctacatna 180  
 gctggaagcc ctggagggcc tctctcgcca gcctccccct tctctccacg ctctccangg 240  
 acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga 300  
 cccatggggc ctgnaaggcc aggtctcct ttgacacat ctctcccgct ctgcctggca 360  
 ggccgtggga tccactantt ctanaacggg cgccaccnec gtgggagctc cagcttttgt 420  
 tccntttaat gaaggttaat tgcncgcttg gcgtaatcat nggtcanaac tntttcctgt 480  
 gtgaaattgt ttntccccctc ncnattccnc ncnacatacn aaccgggaan cataaagtgt 540  
 taaagcctgg gggtngcctn nngaanaaac tnaactcaat taattgcgtt ggctcatggc 600  
 ccgcttttccn ttcnngaaaa ctgtcntccc ctgcnttntt gaatcgggca ccccnnggg 660  
 aaaagcggtt tgcnttttng ggggntcctt ccncttcccc cctcnctaan cctnccgct 720  
 cggtcgttnc nggtngcggg gaangggnat nnnctccnc naagggggng agnnngntat 780  
 ccccaaa 822

<210> 31  
 <211> 799  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(799)  
 <223> n = A,T,C or G

<400> 31

tttttttttt	tttttttggc	gatgctactg	tttaattgca	ggaggtgggg	gtgtgtgtac	60
catgtaccag	ggctattaga	agcaagaagg	aaggagggag	ggcagagcgc	cctgctgagc	120
aacaaaggac	tcctgcagcc	ttctctgtct	gtctcttggc	gcaggcacat	ggggaggcct	180
cccgcagggt	ggggggccacc	agtccagggt	tgggagcact	acanggggtg	ggagtgggtg	240
gtggctggtn	cnaatggcct	gncacanatc	cctacgattc	ttgacacctg	gatttcacca	300
ggggaccttc	tgttctccca	nggnaacttc	ntnnatctcn	aaagaacaca	actgtttctt	360
cngcanttct	ggctgttcat	ggaaagcaca	ggtgtccnat	ttnggctggg	acttggtaca	420
tatgggtccg	gcccacctct	cccntcnaan	aagtaattca	ccccccccc	ccntctnttg	480
cctgggccc	taantacca	caccggaact	canttannta	ttcatcttng	gntgggcttg	540
ntnatcnccn	cetgaangcg	ccaagtgtga	aggccacgcc	gthcccnctc	cccatagnan	600
nttttnncnt	canctaatac	ccccccnggc	aacnatccaa	tcccccccn	tgggggcccc	660
agcccanggc	ccccgnctcg	ggnnnccngn	cncgnantcc	ccaggntctc	ccantcngnc	720
ccnnngcncc	cccgcaacga	gaacanaagg	ntngagccnc	cgcannnnnn	nggtnnccnac	780
ctcgcccccc	ccnnccgngg					799

<210> 32  
 <211> 789  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(789)  
 <223> n = A,T,C or G

<400> 32

tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	60
tttttccnag	ggcagggtta	ttgacaacct	cncgggacac	aancaggctg	gggacaggac	120
ggcaacaggc	tccggcgggc	gcggcgggcg	ccctacctgc	ggtaccaa	ntgcagcctc	180
cgctcccgc	tgatnttct	ctgcagctgc	aggatgccnt	aaaacagggc	ctcgccntn	240
ggtgggcacc	ctgggatttn	aatttccacg	ggcacaatgc	ggtgcganc	cctcaccacc	300
nattaggaat	agtggtnnta	cccnccnccg	ttggcncact	ccccntggaa	accacttntc	360
gcggctccgg	catctggtct	taaaccttgc	aaacnctggg	gocctctttt	tggttantnt	420
ncnngccaca	atcatnactc	agactggcnc	gggctggccc	caaaaaancn	ccccaaaacc	480
ggnccatgtc	ttnnccgggt	tgctgcnatn	tncatcacct	cccgggcnca	ncaggncaac	540
ccaaaagttc	ttgngggccn	caaaaaanct	ccggggggnc	ccagtttcaa	caaagtcac	600
ccccttggcc	cccaaatcct	ccccccgntt	netgggtttg	ggaacccacg	cctctnnctt	660
tggnnggcaa	gntggntccc	ccttcgggce	cccggtgggc	ccnntcttaa	ngaaaacncc	720
ntcctnnnca	ccatcccccc	nngnnacgnc	tancaangna	tccctttttt	tanaaacggg	780
ccccccnccg						789

<210> 33  
 <211> 793  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(793)  
 <223> n = A,T,C or G

&lt;400&gt; 33

gacagaacat	gttgatggt	ggagcacctt	tctatacgac	ttacaggaca	gcagatgggg	60
aattcatggc	tgttgagca	atanaacccc	agttctacga	gctgctgatc	aaaggacttg	120
gactaaagtc	tgatgaactt	cccaatcaga	tgagcatgga	tgattggcca	gaaatgaana	180
agaagtttgc	agatgtattt	gcaaagaaga	cgaaggcaga	gtggtgtcaa	atctttgacg	240
gcacagatgc	ctgtgtgact	ccggttctga	cttttgagga	ggttgttcat	catgatcaca	300
acaangaacg	gggctcgttt	atcaccantg	aggagcagga	cgtgagcccc	cgccctgcac	360
ctctgctgtt	aaacacccca	gccatccctt	ctttcaaaag	ggatccacta	cttctagagc	420
ggnccgccacc	gcggtggagc	tccagctttt	gttcccttta	gtgagggtta	attgcgcgct	480
tggcgtaatc	atggtcatan	ctgtttcctg	tgtgaaattg	ttatccgctc	acaattccac	540
acaacatacg	anccggaagc	atnaaatttt	aaagcctggn	ggtngcctaa	tgantgaact	600
nactcacatt	aattggcttt	gcgctcactg	cccgtttcc	agtccggaaa	acctgtcctt	660
gccagctgcc	nttaatgaat	cnggccaccc	cccggggaaa	aggcngtttg	cttnttgggg	720
cgcncctccc	gctttctcgc	ttcctgaant	ccttcccccc	ggtctttcgg	cttgcggcna	780
acggtatcna	cct					793

&lt;210&gt; 34

&lt;211&gt; 756

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(756)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 34

gccgcgaccg	gcatgtacga	gcaactcaag	ggcgagtggga	accgtaaaag	ccccaatctt	60
ancaagtgcg	gggaanagct	gggtcgactc	aagctagttc	ttctggagct	caacttcttg	120
ccaaccacag	ggaccaagct	gaccaaacag	cagctaattc	tggcccgtga	catactggag	180
atcggggccc	aatggagcat	cctacgcaan	gacatccctt	ccttcgagcg	ctacatggcc	240
cagctcaaat	gctactactt	tgattacaan	gagcagctcc	ccgagtcagc	ctatatgcac	300
cagctcttgg	gcctcaacct	cctcttctctg	ctgtcccaga	accgggtggc	tgantnccac	360
acgganttgg	ancggctgcc	tgcccaanga	catacanacc	aatgtctaca	tcnaccacca	420
gtgtcctgga	gcaatactga	tgganggcag	ctacncaaaa	gtnttcctgg	ccnagggtta	480
catccccgcg	cgagagctac	accttcttca	ttgacatcct	gctcgacact	atcaggggatg	540
aaaatcgcn	ggttgctcca	gaaaggctnc	aanaanatcc	ttttcnctga	aggcccccg	600
atncnctagt	nctagaatcg	gccgcgcac	gcggtgganc	ctccaacctt	tcgttnccct	660
ttactgaggg	ttnattgccg	cccttggegt	tatcatggte	acnccngttn	cctgtgttga	720
aattnttaac	ccccacacat	tccacgcna	cattng			756

&lt;210&gt; 35

&lt;211&gt; 834

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(834)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 35

ggggatctct	anactnacct	gnatgcatgg	ttgtcggtgt	ggtcgctgtc	gatgaanatg	60
aacaggatct	tgcccttgaa	gctctcggt	gctgtnttta	agttgctcag	tctgccgtca	120
tagtcagaca	cncctctggg	caaaaaacan	caggatntga	gtcttgattt	cacctccaat	180
aatcttcnng	gctgtctgct	cggtgaactc	gatgacnang	ggcagctggg	tgtgtntgat	240
aaantccanc	angttctcct	tggtgacctc	cccttcaaa	ttgttcgggc	cttcatcaaa	300
cttctnnaan	angannancc	canctttgtc	gagctggnat	ttgganaaca	cgctactgtt	360

ggaaactgat	cccaaaggt	atgtcatcca	tcgcctctgc	tgccctgcaa	aaacttgctt	420
ggcncaaatc	cgactcccn	tccttgaaag	aagccnatca	cacccccctc	cctggactcc	480
nncaangact	ctnccgctnc	ccntccnng	cagggttgg	ggcannccgg	gccentgcgc	540
ttcttcagcc	agttcacnat	nttcacagc	ccctctgcca	gctgtntat	tccttggggg	600
ggaanccgtc	tctcccttc	tgaannaact	ttgaccgtng	gaatagccgc	gentcnccnt	660
acntnctggg	ccgggttcaa	antccctccn	ttgncnntcn	cctcggggcca	ttctggattt	720
nccnaacttt	ttccttcccc	cncnccnccg	ngtttggnnt	tttcatnggg	ccccaactct	780
gctnttgccc	antcccttgg	gggcntntan	cncnccctnt	ggteccntng	ggcc	834

&lt;210&gt; 36

&lt;211&gt; 814

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(814)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 36

cggnccgttt	ccngccgcgc	cccgtttcca	tgaacnaagg	tccttccang	ttaaatacnn	60
cctagnaaac	attaatgggt	tgctctacta	atacatcata	cnaaccagta	agcctgcccc	120
naacgccaac	tcaggccatt	cctaccaaag	gaagaaaggc	tggtctctcc	accccctgta	180
ggaaaggcct	gccttgtaag	acaccacaat	ncggctgaat	ctnaagtctt	gtgttttact	240
aatggaaaaa	aaaaataaac	aanagggttt	gttctcatgg	ctgcccaccg	cagcctggca	300
ctaaaacanc	ccagcgctca	cttctgcttg	ganaaatatt	ctttgctctt	ttggacatca	360
ggcttgatgg	tatcaactgc	acntttccac	ccagctgggc	ncccttcccc	catntttgtc	420
antganctgg	aaggcctgaa	nottagtctc	caaaagtctc	ngcccacaag	accggccacc	480
aggggagntc	ntttncagtg	gatctgccaa	anantaccn	tatcatcnnt	gaataaaaag	540
gccccgaac	ganatgcttc	cancancctt	taagaccat	aatcctngaa	ccatgggtgcc	600
cttcgggtct	gatccnaaag	gaatgttcct	gggtcccant	ccctcctttg	tttcttacgt	660
tgtnttgac	ccntgctngn	atnaccnaan	tganatcccc	ngaagcacc	tnccctggc	720
atttganttt	cntaaattct	ctgccctacn	nctgaaagca	cnattccctn	ggcnccnaan	780
ggngaactca	agaaggctcn	ngaaaaacca	cncn			814

&lt;210&gt; 37

&lt;211&gt; 760

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(760)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 37

gcatgctgct	cttcctcaaa	gttggtcttg	ttgccataac	aaccaccata	ggtaaagcgg	60
gocagtggt	cgctgaagg	gttgtagtac	cagcgcgga	tgctctcctt	gcagagtect	120
gtgtctggca	ggtccacgca	atgccctttg	tcactgggga	aatggatgcg	ctggagctcg	180
tcnaanccac	tcgtgtattt	ttcacangca	gcctcctccg	aagcntccgg	gcagttgggg	240
gtgtcgtcac	actccactaa	actgtcgatn	cancagccca	ttgctgcagc	ggaactgggt	300
gggctgacag	gtgccagaac	acactggatn	ggcctttcca	tggaagggcc	tgggggaaat	360
cncctnancc	caaactgcct	ctcaaaggcc	accttgcaac	ccccgacagg	ctagaaatgc	420
actcttcttc	ccaaaggtag	ttgttcttgt	tgcccaagca	ncctccanca	aacccaaaanc	480
ttgcaaaatc	tgctccgtgg	gggtcatnnn	taccanggtt	ggggaaaana	acccggcngn	540
ganccnccct	gtttgaatgc	naaggnaata	atcctcctgt	cttgcttggg	tggaanagca	600
caattgaact	ggttaacntt	ggccgngttc	cncnngggtg	gtctgaaact	aatcacgcgc	660
actggaaaaa	ggtangtgcc	ttccttgaat	tcccaaantt	cccctngntt	tgggtntttt	720



ctectctncc ctaaaaatcg tnttcccccc cnttanggcg

760

<210> 38  
 <211> 724  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(724)  
 <223> n = A, T, C or G

<400> 38  
 tttttttttt tttttttttt tttttttttt ttttttaaaaa cccctcccat tgaatgaaaa 60  
 cttccnfaaat tgtccaaccc cctcnnccaa atnnccattt ccgggggggg gttccaaacc 120  
 caaattaatt ttgganttta aattaaatnt tnattnnggg aanaanccaa atgtnaagaa 180  
 aatttaaccc attatnaact taaatnccctn gaaacccntg gnttccaaaa atttttaacc 240  
 cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaagggt 300  
 ngattttaaac ccccttnant tnttttnacc cnnngctnaa ntatttnngt tccgggtgtt 360  
 tectnttaan cntnggtaac tcccgntaat gaannnccct aanccaatta aaccgaattt 420  
 tttttgaatt ggaaattccn ngggaattna ccgggggtttt tcccnttttg gggccatncc 480  
 ccncttttcg ggggtttgggn ntagggttgaa tttttnnang nccccaaaaa ncccccaana 540  
 aaaaaactcc caagnnttaa ttngaantnc ccccttccca ggcctttttg gaaaggnggg 600  
 tttntggggg ccngggantt cnttcccccn ttncncccc cccccnggt aaanggttat 660  
 ngnttttggg ttttgggccc cttnanggac cttccggatn gaaattaaat ccccggnccg 720  
 gccg 724

<210> 39  
 <211> 751  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(751)  
 <223> n = A, T, C or G

<400> 39  
 tttttttttt tttttctttg ctcacattta atttttattt tgattttttt taatgctgca 60  
 caacacaata tttatttcat ttgtttcttt tatttcatth tatttgtttg ctgctgctgt 120  
 tttatttatt ttactgaaa gtgagaggga acttttgttg ccttttttcc tttttctgta 180  
 ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aaggggggtt 240  
 cgcaaaatca ctcgggggaa nggaaagggt gctttgttaa tcatgcccta tgggtgggtga 300  
 ttaactgctt gtacaattac ntthcacttt taattaattg tgctnaangc ttttaattana 360  
 cttgggggtt ccctcccan accaaccnna ctgacaaaaa gtgccngccc tcaaatnatg 420  
 tcccggcnnt cnttgaaaca cacngcngaa ngttctcatt ntcccncnc caggtnaaaa 480  
 tgaagggtta ccatntttta cncacctcc acntggcnnn gcctgaatcc tcnaaaancn 540  
 cctcaancn aattnctnng ccccggtcnc gcntnngtcc cncocgggct ccgggaantn 600  
 cccccnga anncnntnnc naacnaaatt ccgaaaatat tccnntenc tcaattcccc 660  
 cnnagactnt cctcnncnan cncaattttc tttntntcac gaacnognnc cnnaaaatgn 720  
 nnnncnctc cncntngtccn naatcnccan c 751

<210> 40  
 <211> 753  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature  
 <222> (1)...(753)  
 <223> n = A,T,C or G

<400> 40  
 gtggtatttt ctgtaagatc aggtgttcct cctcgtagg tttagaggaa acaccctcat 60  
 agatgaaaac ccccccgaga cagcagcact gcaactgcc aagcagccgg gttagggggg 120  
 cgccctatgc acagctgggc ccttgagaca gcagggttc gatgtcaggc tcgatgtcaa 180  
 tgggtctggaa gggcggtctg tacctgcgta ggggcacacc gtcagggcc accaggaact 240  
 tctcaaagtt ccaggcaacn tcgttgcgac acaccggaga ccaggtgatn agcttggggg 300  
 cggtcataa cgcgggtggcg tcgtcgtctg gagctggcg ggccctccgc aggaaggcna 360  
 ataaaagggt cgcggggcga ccgttcact cgcacttctc naanaccatg angttgggct 420  
 cnaaccacc accannccgg acttccttga nggaattccc aaatctcttc gntcttgggc 480  
 ttctnctgat gccctanctg gttgccnngn atgccaanca nccccaancc ccgggggtct 540  
 aaanacccn cctcctcctt tcatctgggt tntntcccc ggacntggg tctctcaag 600  
 gganccata tctcnaccan tactcacnt nccccccnt gnnaccanc cttctanngn 660  
 ttccncccg nccctctggc cntcaaanah gcttnacna cctgggtctg ccttcccccc 720  
 tnccctatct gnaccccn n tttgtctcan tnt 753

<210> 41  
 <211> 341  
 <212> DNA  
 <213> Homo sapien

<400> 41  
 actatatcca tcacaacaga catgcttcat cccatagact tcttgacata gtttcaaag 60  
 agtgaacca tccttgattt atatacatat atgttctcag tattttggga gcccttccac 120  
 ttctttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt 180  
 tatagcttgt ttacgtagta agtttttgaa gtctacattc aatccagaca cttagttgag 240  
 tggtaaactg tgatttttaa aaaatatcat ttgagaatat tctttcagag gtattttcat 300  
 ttttactttt tgattaattg tgttttatat attagggtag t 341

<210> 42  
 <211> 101  
 <212> DNA  
 <213> Homo sapien

<400> 42  
 acttactgaa tttagttctg tgctcttcct tatttagtgt tgtatcataa atactttgat 60  
 gtttcaaaca ttctaaataa ataattttca gtggcttcat a 101

<210> 43  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 43  
 acatctttgt tacagtctaa gatgtgttct taaatcacca ttccttctg gtcctcaccc 60  
 tccagggtgg tctcacactg taattagagc tattgaggag tctttacagc aaattaagat 120  
 tcagatgcct tgctaagtct agagttctag agttatgtt cagaaagtct aagaaacca 180  
 cctcttgaga ggtcagtaaa gaggacttaa tatttcatat ctacaaaatg accacaggat 240  
 tggatacaga acgagagtta tcttgataa ctcagagctg agtacctgcc cggggggccg 300  
 tcgaa 305

<210> 44  
 <211> 852  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(852)  
 <223> n = A,T,C or G

<400> 44  
 acataaatat cagagaaaag tagtctttga aatattttacg tccaggagtt ctttgtttct 60  
 gattatttgg tgtgtgtttt ggtttgtgtc caaagtattg gcagcttcag ttttcatttt 120  
 ctctccatcc tcgggcattc ttcccaaatt tatataccag tcttcgtcca tccacacgct 180  
 ccagaatttc tctttttag tagtatctca tagctcggct gagcttttca taggtcatgc 240  
 tgctgttggt cttcttttta ccccatagct gagccactgc ctctgatttc aagaacctga 300  
 agacgccctc agatcgggtc tcccatttta ttaatcctgg gttcttgtct gggttcaaga 360  
 ggatgtcgcg gatgaattcc cataagttag tccctctcgg gttgtgcttt ttggtgtggc 420  
 acttgfcagg ggggtcttgc tcttttttca tatcaggtag ctctgcaaca ggaaggtagac 480  
 tgggtggtgt catggagatc tgagcccgge agaaagtatt gctgtccaac aaatctactg 540  
 tgctaccata gttggtgtca tataaatagt tctngtcttt ccagggtgtc atgatggaag 600  
 gctcagtttg ttcagtcttg acaatgacat tgtgtgtgga ctggaacagg tcactactgc 660  
 actggccgtt ccacttcaga tgctgcaagt tgctgtagag gagntgcccc gccgtccctg 720  
 ccgccgggt gaactcctgc aaactcatgc tgcaaagggt ctgccggtg atgtcgaact 780  
 cntggaaagg gatacaattg gcatccagct ggttggtgtc caggaggtga tggagccact 840  
 cccacacctg gt 852

<210> 45  
 <211> 234  
 <212> DNA  
 <213> Homo sapien

<400> 45  
 acaacagacc cttgctcgtc aacgacctca tgctcatcaa gttggacgaa tccgtgtccg 60  
 agtctgacac catccggagc atcagcattg ctctgcagtg ccctaccgcg gggaaactctt 120  
 gcctcgtttc tggctggggg ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg 180  
 tgaacgtgtc ggtggtgtct gaggaggtct gcagtaagct ctatgaccg ctgt 234

<210> 46  
 <211> 590  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(590)  
 <223> n = A,T,C or G

<400> 46  
 actttttatt taaatgttta taaggcagat ctatgagaat gatagaaaac atggtgtgta 60  
 atttgatagc aatattttgg agattacaga gttttagtaa ttaccaatta cacagttaaa 120  
 aagaagataa tatattccaa gcanatacaa aatatctaata gaaagatcaa ggcaggaaaa 180  
 tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta 240  
 aaagctttca aaanaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat 300  
 caggataaan aactgaagg canaaagaat taattttcac ttcattgtaac ncacccanat 360  
 ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aaggctcttc 420  
 tggctcttaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag 480  
 ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct 540  
 gccttccttt gaggagactt catctcactg gccaacactc agtcacatgt 590

<210> 47  
 <211> 774

<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(774)  
 <223> n = A,T,C or G

<400> 47  
 acaagggggc ataatgaagg agtggggana gatttttaaag aaggaaaaaa aacgaggccc 60  
 tgaacagaat tttcctgnac aacggggcctt caaaataatt ttcttgggga gggtcaagac 120  
 gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg 180  
 cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa 240  
 aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggtct 300  
 cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctctgtgtg 360  
 ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgctgat cctgcgtggc 420  
 ccacactcct tgaacacaca tccccaggtt atattcctgg acatggctga acctoctatt 480  
 cctacttccg agatgccttg ctccctgcag cctgtcaaaa tcccactcac cctocaaacc 540  
 acggcatggg aagcctttct gacttgccctg attactccag catcttggaa caatccctga 600  
 ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttgagacc 660  
 aggctgctgg cttcaaattn tggctcattt acgagctatg ggaccttggg caagtnatct 720  
 tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt 774

<210> 48  
 <211> 124  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(124)  
 <223> n = A,T,C or G

<400> 48  
 canaaattga aattttataa aaaggcattt ttctcttata tccataaaat gatataattt 60  
 ttgcaantat anaaatgtgt cataaattat aatgttcctt aattacagct caacgcaact 120  
 tggt 124

<210> 49  
 <211> 147  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(147)  
 <223> n = A,T,C or G

<400> 49  
 gccgatgcta ctatttttatt gcaggaggtg ggggtgtttt tattattctc tcaacagctt 60  
 tgtggctaca ggtgggtgtc gactgcatna aaaanttttt tacgggtgat tgcaaaaatt 120  
 ttagggcacc catatcccaa gcantgt 147

<210> 50  
 <211> 107  
 <212> DNA  
 <213> Homo sapien

<400> 50  
 acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatggctt gatatatattgc 60  
 atggtttgag gttaggagga gttaggcata tgttttggga gaggggt 107

<210> 51  
 <211> 204  
 <212> DNA  
 <213> Homo sapien

<400> 51  
 gtcctaggaa gtctagggga cacacgactc tggggtcacg gggccgacac acttgcaagg 60  
 cgggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag 120  
 gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgcc cacttgcca 180  
 cctccctttt gggaccagca atgt 204

<210> 52  
 <211> 491  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(491)  
 <223> n = A,T,C or G

<400> 52  
 acaaagataa catttatctt ataacaaaaa tttgatagtt ttaaaggtta gtatttgtta 60  
 gggatatttc caaaagacta aagagataac tcaggtaaaa agttagaaat gtataaaaca 120  
 ccatcagaca ggttttttaa aaacaacata ttacaaaatt agacaatcat ctttaaaaaa 180  
 aaaacttctt gtatcaattt cttttgttca aaatgactga cttaantatt tttaaatatt 240  
 tcanaaacac ttcttcaaaa attttcaana tggtagcttt canatgtnc ctcagtccca 300  
 atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc 360  
 atgcaacagt gtcttttctt tnttttttct tttttttttt ttacaggcac agaaactcat 420  
 caattttatt tggataacaa aggggtctcca aattatatgt aaaaataaat ccaagttaat 480  
 atcactcttg t 491

<210> 53  
 <211> 484  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(484)  
 <223> n = A,T,C or G

<400> 53  
 acataattta gcagggctaa ttaccataag atgctattta ttaanaggtn tatgatctga 60  
 gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac 120  
 actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct 180  
 caatcaaadc tctacataac actatagtaa ttaaaacggt aaaaaaaagt gttgaaatct 240  
 gcaactagat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc 300  
 agcttttgant ttctttgtgc tgatangagg aaaggctgaa ttaccttggt gcctctccct 360  
 aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncg 420  
 tanccttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncggatgttc 480  
 cant 484

<210> 54

<211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 54  
 actaaacctc gtgcttgtga actccataca gaaaacgggtg ccatcootga acacgggtgg 60  
 ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag 120  
 tctatgtcct ctcaagtgcc tttttgtttg t 151

<210> 55  
 <211> 91  
 <212> DNA  
 <213> Homo sapien

<400> 55  
 acctggcttg tctccgggtg gttcccggtg cccccacgg tccccagaac ggacactttc 60  
 gccctccagt ggatactcga gccaaagtgg t 91

<210> 56  
 <211> 133  
 <212> DNA  
 <213> Homo sapien

<400> 56  
 ggcggatgtg cgttggttat atacaaatat gtcattttat gtaagggtact tgagtatact 60  
 tggatttttg gtatctgtgg gttgggggga cgggccagga accaatacc catggatacc 120  
 aagggacaac tgt 133

<210> 57  
 <211> 147  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(147)  
 <223> n = A,T,C or G

<400> 57  
 actctggaga acctgagccg ctgctccgcc tctgggatga ggtgatgcan gngtgggocg 60  
 gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana 120  
 tctcantggg ctggatncat gcagggt 147

<210> 58  
 <211> 198  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(198)  
 <223> n = A,T,C or G

<400> 58  
 acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc 60  
 tgattacata catttatcct ttaaaaaaga tgtaaatcctt aatttttatg ccatctatta 120  
 atttaccat gagttacctt gtaaagtaga agtcatgata gcactgaatt ttaactagtt 180  
 ttgacttcta agtttggt 198

<210> 59  
 <211> 330  
 <212> DNA  
 <213> Homo sapien

<400> 59  
 acaacaaatg ggttgtgagg aagtcttatac agcaaaaactg gtgatggcta ctgaaaagat 60  
 ccattgaaaa ttatcattaa tgatttttaa tgacaagtta tcaaaaactc actcaatttt 120  
 cacctgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa 180  
 tacagtcaat aaatgacaaa gccagggcct acaggtggtt tccagacttt ccagaccag 240  
 cagaaggaat ctattttatc acatggatct ccgctctgtc tcaaaatacc taatgatatt 300  
 tttcgtcttt attggacttc ttgaagagt 330

<210> 60  
 <211> 175  
 <212> DNA  
 <213> Homo sapien

<400> 60  
 accgtgggtg ctttctacat tcttgacggc tccttcacca acatctggtt ctacttcggc 60  
 gtcgtgggct ctttctctt catctcctc cagctggtgc tgctcatcga ctttgccgac 120  
 tcctggaacc agcgtggtg gggcaaggcc gaggagtgcg attcccgtgc ctggt 175

<210> 61  
 <211> 154  
 <212> DNA  
 <213> Homo sapien

<400> 61  
 accccacttt tcttctgtg agcagtctgg acttctcact gctacatgat gaggggtgagt 60  
 ggtgtgtgct cttcaacagt atctcctcct ttccggatct gctgagccgg acagcagtgc 120  
 tggactgcac agccccgggg ctccacattg ctgt 154

<210> 62  
 <211> 30  
 <212> DNA  
 <213> Homo sapien

<400> 62  
 cgctcgagcc ctatagttag tcgtattaga 30

<210> 63  
 <211> 89  
 <212> DNA  
 <213> Homo sapien

<400> 63  
 acaagtcatt tcagcaccct ttgctcttca aaactgacca tcttttatat ttaatgcttc 60  
 ctgtatgaat aaaaatgggt atgtcaagt 89

<210> 64  
 <211> 97  
 <212> DNA  
 <213> Homo sapien

<400> 64  
 accggagtaa ctgagtcggg acgctgaatc tgaatccacc aataaataaa ggttctgcag 60

aatcagtgc tccaggattg gtccttggat ctgggggt

97

<210> 65  
 <211> 377  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(377)  
 <223> n = A,T,C or G

<400> 65  
 acaacaanaa ntcccttctt taggcoactg atggaaacct ggaacccctt tttgatggca 60  
 gcatggcgtc ctaggccttg acacagcggc tgggggttgg gctntoccaa accgcacacc 120  
 ccaaccctgg tctaccaca nttctggcta tgggctgtct ctgccactga acatcagggt 180  
 tcggtcataa natgaaatcc caanggggac agaggtcagt agaggaagct caatgagaaa 240  
 ggtgctgttt gctcagccag aaaacagctg cctggcatto gccgctgaac tatgaacccg 300  
 tgggggtgaa ctaccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag 360  
 gggcgaggag agcatgt 377

<210> 66  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 66  
 acgcctttcc ctcagaattc aggggaagaga ctgtcgctg ccttctccg ttgttgctg 60  
 agaaccctg tgcccttcc caccatatcc accctcgtc catctttgaa ctcaaacag 120  
 aggaactaac tgcaccctgg tctctctccc agtccccagt tcaccctcca tccctcacct 180  
 tctccactc taagggatat caacactgcc cagcacagg gccctgaatt tatgtggttt 240  
 ttatatattt tttaataaga tgcactttat gtcatttttt aataaagtct gaagaattac 300  
 tggtt 305

<210> 67  
 <211> 385  
 <212> DNA  
 <213> Homo sapien

<400> 67  
 actacacaca ctccacttgc ctttgtgaga cactttgtcc cagcacttta ggaatgctga 60  
 ggtcggacca gccacatctc atgtgcaaga ttgccagca gacatcagg ctgagagttc 120  
 cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc 180  
 tgtgtgtgctc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg 240  
 ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg 300  
 cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgcccatac 360  
 catagtttct gtgctagtgg accgt 385

<210> 68  
 <211> 73  
 <212> DNA  
 <213> Homo sapien

<400> 68  
 acttaaccag atatattttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa 60  
 gtttttttaa tgg 73

<210> 69



<211> 536  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(536)  
 <223> n = A,T,C or G

<400> 69  
 actagtcag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctctgcagc 60  
 tccagctttg tgctctgcct ctgaggagac catggcccag catctgagta ccctgctgct 120  
 cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat 180  
 cccgggtggc atctataacg cagacotcaa tgatgagtgg gtacagcgtg cccttcactt 240  
 cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgtgcgggt 300  
 actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg 360  
 ccgaaccata tgtaccaagt cccagcccaa ctgggacacc tgtgccttcc atgaacagcc 420  
 agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca 480  
 gaangtcctt gggtgaaatc cagggtgtcaa gaaatcctan ggatctgttg ccaggc 536

<210> 70  
 <211> 477  
 <212> DNA  
 <213> Homo sapien

<400> 70  
 atgacccta acagggggccc tctcagccct cctaatagacc tccggcctag ccatgtgatt 60  
 tcacttccac tccataacgc tctcataact aggcctacta accaacacac taaccatata 120  
 ccaatgatgg cgcgatgtaa cagagaaaag cacataccaa ggccaccaca caccacctgt 180  
 ccaaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc 240  
 agggattttt ctgagccttt taccactcca gcctagcccc taccacccaa ctaggagggc 300  
 actggccccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaacacat 360  
 ccgtattact cgcacagga gtatcaatca cctgagctca ccatagtcta atagaaaaca 420  
 accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt 477

<210> 71  
 <211> 533  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(533)  
 <223> n = A,T,C or G

<400> 71  
 agagctatag gtacagtgtg atctcagctt tgcaaacaca ttttctacat agatagtact 60  
 aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta 120  
 tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat 180  
 attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt 240  
 taaataaagg tttgtcatct ttaaaaatac agcaatatgt gactttttta aaaagctgtc 300  
 aaatagggtg gaccctacta ataattatta gaaatacatt taaaaacatc gagtacctca 360  
 agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg 420  
 cttcgttaatt ttggagtang aggttccttc ctcaattttg tattttttaa aagtacatgg 480  
 taaaaaaaaa aattcacaaac agtatataag gctgtaaaaat gaagaattct gcc 533

<210> 72  
 <211> 511

<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(511)  
<223> n = A,T,C or G

<400> 72

tattacggaa	aaacacacca	cataattcaa	ctancaaaga	anactgcttc	agggcgtgta	60
aaatgaaagg	ottccaggca	gttatctgat	taaagaacac	taaaagaggg	acaaggctaa	120
aagccgcagg	atgtctacac	tatancaggc	gctatttggg	ttggctggag	gagctgtgga	180
aaacatggan	agattggtgc	tgganatcgc	cgtggctatt	cctcattggt	attacanagt	240
gaggttctct	gtgtgcccac	tggtttgaaa	accgttctnc	aataatgata	gaatagtaca	300
cacatgagaa	ctgaaatggc	ccaaacccag	aaagaaagcc	caactagatc	ctcagaanac	360
gcttctaggg	acaataaccg	atgaagaaaa	gatggcctcc	ttgtgcccc	gtctgttatg	420
atttctctcc	attgcagcna	naaacccgtt	cttctaagca	aacncagggtg	atgatggcna	480
aaatacaccc	cctcttgaag	naccnggagg	a			511

<210> 73  
<211> 499  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(499)  
<223> n = A,T,C or G

<400> 73

cagtgccagc	actggtgcca	gtaccagtac	caataacagt	gccagtgcc	gtgccagcac	60
cagtgggtggc	ttcagtgtctg	gtgccagcct	gaccgccact	ctcacatttg	ggctcttgcg	120
tggccttggg	ggagctgggtg	ccagcaccag	tggcagctct	ggtgcctgtg	gtttctccta	180
caagtgagat	tttagatatt	gttaatcctg	ccagtctttc	tcttcaagcc	aggggtgcac	240
ctcagaaacc	tactcaacac	agcactctag	gcagccacta	tcaatcaatt	gaagttgaca	300
ctctgcatta	aatctatttg	ccattttctga	aaaaaaaaaa	aaaaaaagg	cgcccgctcg	360
antctagagg	gcccgtttaa	acccgctgat	cagcctcgac	tgtgccttct	anttgccagc	420
catctgttgt	ttgcccctcc	cccgntgcct	tccttgacct	tggaaagtgc	cactccact	480
gtcctttcct	aantaaaat					499

<210> 74  
<211> 537  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(537)  
<223> n = A,T,C or G

<400> 74

tttcatagga	gaacacactg	aggagatact	tgaagaattt	ggattcagcc	gcgaagagat	60
ttatcagctt	aactcagata	aaatcattga	aagtaataag	gtaaaagcta	gtctctaact	120
tccaggccca	cggctcaagt	gaatttgaat	actgcattta	cagtgtagag	taacacataa	180
cattgtatgc	atggaaacat	ggaggaacag	tattacagtg	tcctaccact	ctaatacaga	240
aaagaattac	agactctgat	tctacagtga	tgattgaatt	ctaaaaatgg	taatcattag	300
ggcttttgat	ttataanaact	ttgggtactt	atactaaatt	atggtagtta	tactgccttc	360
cagtttgctt	gatataattg	ttgatattaa	gattcttgac	ttatattttg	aatgggttct	420

actgaaaaan gaatgatata ttcttgaaga catcgatata catttattta cactcttgat 480  
tctacaatgt agaaaatgaa ggaaatgccc caaatgtat ggtgataaaa gtcccgt 537

<210> 75  
<211> 467  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(467)  
<223> n = A,T,C or G

<400> 75  
caaandcaat tgttcaaaag atgcaaata tacactactg ctgcagctca caaacacctc 60  
tgcattattac acgtacctcc tctgtctcct caagtagtgt ggtctatatt gccatcatca 120  
cctgtctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg 180  
tggcacaagg aggccatctt ttctcatcgt gttattgtcc ctagaagcgt cttctgagga 240  
tctagttggg ctttctttct ggggttgggc catttcantt ctcatgtgtg tactattcta 300  
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa 360  
caatgaggaa tagccacggg gatctccagc accaaatctc tccatgttnt tccagagctc 420  
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn 467

<210> 76  
<211> 400  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(400)  
<223> n = A,T,C or G

<400> 76  
aagctgacag cattcgggcc gagatgtctc gctccgtggc cttagctgtg ctgcgctac 60  
tctctctttc tggcctggag gctatccagc gtactccaaa gattcaggtt tactcacgtc 120  
atccagcaga gaattgaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat 180  
ccgacattga agtgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag 240  
acttgtcttt cagcaaggac tggcttttct atctcttgta ctacactgaa ttcaccccca 300  
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng 360  
ttnagtggga tctganacatg taagcagcan catgggaggt 400

<210> 77  
<211> 248  
<212> DNA  
<213> Homo sapien

<400> 77  
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct 60  
ccagctgccc cggcggggga tgcgaggctc ggagcaccct tgcccggctg tgattgtctc 120  
caggcactgt tcatctcagc ttttctgtcc ctttgtctcc ggcaagcgt tctgtgaaa 180  
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgtctccac ccgaaaaaaa 240  
aaaaaaaa 248

<210> 78  
<211> 201  
<212> DNA  
<213> Homo sapien

<400> 78  
 actagtccag tgtggtggaa ttccattgtg ttggggcccaa cacaatggct acctttaaca 60  
 tcacccagac ccgcctctgc ccgtgcccca cgctgctgct aacgacagta tgatgcttac 120  
 tctgctactc ggaaactatt tttatgtaat taatgtatgc tttcttgttt ataaatgcct 180  
 gatttaaaaa aaaaaaaaaa a 201

<210> 79  
 <211> 552  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(552)  
 <223> n = A,T,C or G

<400> 79  
 tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg 60  
 tttaggcagt gctagtaatt tctctgtaat gattctgtta ttactttcct attctttatt 120  
 cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag 180  
 tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt 240  
 atgcaagtta gtaattactc agggtttaact aaattacttt aatatgctgt tgaacctact 300  
 ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga 360  
 taatattcta tgttctaaaa gttgggctat acataaanta tnaagaaata tggaatttta 420  
 ttcccaggaa tatgggggtc atttatgaat antaccggg anagaagttt tgantnaaac 480  
 cngtttttgt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa 540  
 aaaaaaaaaa aa 552

<210> 80  
 <211> 476  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(476)  
 <223> n = A,T,C or G

<400> 80  
 acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga 60  
 ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct 120  
 cacacagact ccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt 180  
 gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta 240  
 aggttaaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac 300  
 tctttctaagt cctcttccag cctcactttg agtcctcctt gggggttgat aggaantntc 360  
 tcttggtttt ctcaataaaa tctctatoca tctcatgttt aatttggtag gcntaaaaat 420  
 gctgaaaaaa ttaaaatggt ctggtttcnc tttaaaaaaa aaaaaaaaaa aaaaaa 476

<210> 81  
 <211> 232  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(232)  
 <223> n = A,T,C or G

&lt;400&gt; 81

tttttttttg	tatgccntcn	ctgtggngtt	attgttgctg	ccaccctgga	ggagcccagt	60
ttcttctgta	tctttctttt	ctgggggata	ttcttggtc	tgccctcca	ttcccagcct	120
ctcatcccca	tcttgcaactt	ttgctagggg	tggaggcgct	ttcttggtag	cccctcagag	180
actcagtcag	cggaataag	tcttaggggt	gggggtgtg	gcaagccggc	ct	232

&lt;210&gt; 82

&lt;211&gt; 383

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(383)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 82

aggcgggagc	agaagctaaa	gccaaagccc	aagaagagtg	gcagtgccag	cactggtgcc	60
agtaccagta	ccaataacat	gccagtgcc	gtgccagcac	cagtgggtggc	ttcagtgtctg	120
gtgccagcct	gaccgccact	ctcacatttg	ggctcttcgc	tggccttggt	ggagctgggtg	180
ccagcaccag	tggcagctct	ggtgcctgtg	gtttctccta	caagtggat	tttagatatt	240
gttaatcctg	ccagtctttc	tcttcaagcc	agggtgcata	ctcagaaacc	tactcaacac	300
agcactctng	gcagccacta	tcaatcaatt	gaagttgaca	ctctgcatta	aatctatttg	360
ccatttcaaa	aaaaaaaaaa	aaa				383

&lt;210&gt; 83

&lt;211&gt; 494

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(494)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 83

accgaattgg	gaccgctggc	ttataagcga	tcatgtcttc	cagtattacc	tcaacgagca	60
gggagatcga	gtctatacgc	tgaagaaatt	tgaccgatg	ggacaacaga	cctgctcagc	120
ccatcctgct	cggttctccc	cagatgacaa	atactctcga	caccgaatca	ccatcaagaa	180
acgcttcaag	gtgctcatga	cccagcaacc	gcgccctgtc	ctctgagggg	ccttaaactg	240
atgtcttttc	tgccacctgt	taccctctcg	agactccgta	accaaactct	tgggactgtg	300
agccctgatg	cctttttgcc	agccatactc	tttggcntcc	agtctctcgt	ggcgattgat	360
tatgcttggtg	tgaggcaatc	atggtggcat	cacccatnaa	gggaacacat	ttganttttt	420
tttncatat	tttaaattac	naccagaata	nttcagaata	aatgaattga	aaaactctta	480
aaaaaaaaaa	aaaa					494

&lt;210&gt; 84

&lt;211&gt; 380

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(380)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 84

```

gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca      60
agtatcctgc gccgcgtctt ctaccgtccc tacctgcaga tcttcgggca gattccccag      120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg      180
gcacaccctc ctggggccca ggcgggcacc tgcgtctccc agtatgcaa ctggctggtg      240
gtgctgctcc tgcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg      300
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc      360
agcgttncgg cctcatccgg

```

```

<210> 85
<211> 481
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

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```

<400> 85
gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggctctctgc ttcataccgc      60
tnccatcgtc atactgtagg ttggccacca cctcctgcat cttggggcgg ctaatatcca      120
ggaaactctc aatcaagtca ccgctcnatna aacctgtggc tggttctgtc ttccgctcgg      180
tgtgaaagga tctccagaag gagtgcctga tcttccccac actttttagt actttattga      240
gtcgattctg catgtccagc aggagggtgt accagctctc tgacagttag gtcaccagcc      300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggg gnagtctcac      360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggngaa      420
aaagaacacc tcctggaagt gctngccgct cctcgtcent tggtggnngc gentnccttt      480
t

```

```

<210> 86
<211> 472
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

```

```

<400> 86
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt      60
acttggaana gcaacttnaa gcctggacac tggattataa attcacaata tgcaacactt      120
taaacagtgt gtcaatctgc tcccttaactt tgatcatcacc agtctgggaa taagggtatg      180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga      240
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gtagccaat tcactttctt      300
catgggacag agccatttga tttaaaaaagc aaattgcata atattgagct ttgggagctg      360
atatntgagc ggaagantag cctttctact tcaccagaca caactccttt catattggga      420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg      472

```

```

<210> 87
<211> 413
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(413)
<223> n = A,T,C or G

```

<400> 87  
 agaaaccagt atctctnaaa acaacctctc ataccttggtg gacctaatTT tgtgtgcgtg 60  
 tgtgtgtgcg cgcataattat atagacaggc acatcttttt tacttttgta aaagcttatg 120  
 cctcttttgt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct 180  
 ttgtcttctg tgtaaagtgt actagagaaa acacctatnt tatgagtcaa tctagttngt 240  
 tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc cttgactagg 300  
 ggggacaaaag aaaagcnaaa ctgaacatna gaaacaattn cctggtgaga aattncataa 360  
 acagaaattg ggtngtatat tgaaanang catcattnaa acgttttttt ttt 413

<210> 88

<211> 448

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(448)

<223> n = A,T,C or G

<400> 88  
 cgcagcgggt cctctctatc tagctccagc ctctcgctg ccccaactccc cgcgtcccgc 60  
 gtcctagccn accatggcgg ggccctgog cgcctcgctg ctctgctgg ccactcctggc 120  
 cgtggccctg gccgtgagcc ccgcggccgg ctccagctcc ggcaagccgc cgcgcctggt 180  
 gggaggccca tggacccgc gtggaagaag aagggtgtgcg gcgtgcactg gactttgccg 240  
 tcggcnanta caacaaaccc gcaacnactt ttaccnagcn cgcgctgcag gttgtgccgc 300  
 cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng 360  
 tttaccagaa ccnagccaat tngaacaatt nccctccat aacagcccct tttaaaaagg 420  
 gaancantcc tgnctctttc caaatttt 448

<210> 89

<211> 463

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(463)

<223> n = A,T,C or G

<400> 89  
 gaattttgtg cactggccac tgtgatggaa ccattggggc aggatgcttt gagtttatca 60  
 gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaatgtca aaaaattagc 120  
 agagggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaagtt 180  
 ctcaagtaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcatc 240  
 tttnatgttn agacttgect ctntnaaatt gcttttgtnt tctgcaggta ctatctgtgg 300  
 ttttaaaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn 360  
 aattctctcc ccatannaaa acccangccc ttggganaat ttgaaaaang gntccttcnn 420  
 aattcnnana anttcagntn tcatacaaca naacngganc ccc 463

<210> 90

<211> 400

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(400)

<223> n = A, T, C or G

<400> 90

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tcttcaccag	tcacatcttc	taggaccttt	ttggattcag	ttagtataag	ctcttcact	180
tcctttgtta	agacttcctc	tggtaaagtc	ttaggttttg	tagaaaggaa	tttaattgct	240
cgtttctctaa	caatgtcctc	tccttgaagt	atttggctga	acaaccacc	tnaagtcct	300
ttgtgcatcc	attttaaata	tacttaatag	ggcattggtn	cactaggtta	aattctgcaa	360
gagtcactctg	tctgcaaaaag	ttgcgttagt	atatctgcca			400

<210> 91

<211> 480

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(480)

<223> n = A, T, C or G

<400> 91

gagctcggat	ccaataatct	ttgtctgagg	gcagcacaca	tatncagtgc	catggnaact	60
ggtctacccc	acatgggagc	agcatgccgt	agntatataa	ggtcattccc	tgagtcagac	120
atgcctcttt	gactaccgtg	tgccagtgtc	ggtgattctc	acacacctcc	nncgctctt	180
tgtggaaaaa	ctggcacttg	nctggaacta	gcaagacatc	acttacaat	tcacccacga	240
gacacttgaa	aggtgttaaca	aagcgactct	tgcatgtctt	tttgtccctc	cggcaccagt	300
tgtcaatact	aacccgctgg	tttgctcca	tcacatttgt	gatctgtagc	tctggataca	360
tctcctgaca	gtactgaaga	acttctctt	ttgtttcaaa	agcaactctt	ggtgcctgtt	420
ngatcagggt	cccatttccc	agtcogaatg	ttcacatggc	atatnttact	tcocacaaaa	480

<210> 92

<211> 477

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(477)

<223> n = A, T, C or G

<400> 92

atacagccca	natcccacca	cgaagatgcg	cttggtgact	gagaacotga	tgcggtcact	60
ggtcccgtg	tagccccagc	gactctccac	ctgctggaag	cggttgatgc	tgactcctt	120
cccacgcagg	cagcagcggg	gccggtcaat	gaactccact	cgtggcttgg	ggttgacggt	180
taantgcagg	aagaggctga	ccacctcgcg	gtccaccagg	atgcccgact	gtgcgggacc	240
tgacgcgaaa	ctcctcgatg	gtcatgagcg	ggaagcgaat	gangcccagg	gccttgccca	300
gaaccttccg	cctgttctct	ggcgtcacct	gcagctgctg	cggctnacac	tcggcctcgg	360
accagcggag	aaacggcggt	gaacagccgc	acctcacgga	tgcccantgt	gtcgcgctcc	420
aggaacggcn	ccagcgtgtc	caggtcaatg	tcggtgaanc	ctccgcgggt	aatggcg	477

<210> 93

<211> 377

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature



&lt;222&gt; (1)...(377)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 93

gaacggctgg	accttgccctc	gcattgtgct	gctggcagga	ataccttggc	aagcagctcc	60
agtccgagca	gccccagacc	gctgccgccc	gaagctaagc	ctgcctctgg	ccttcccctc	120
cgcctcaatg	cagaaccant	agtgggagca	ctgtgttttag	agttaagagt	gaacactgtg	180
tgattttact	tggaatttc	ctctgttata	tagcttttcc	caatgcta	ttccaaacaa	240
caacaacaaa	ataacatgtt	tgctgttna	gttgataaaa	agtangtgat	tctgtatnta	300
aagaaaatat	tactgttaca	tatactgctt	gcaanttctg	tatttattgg	tnctctggaa	360
ataaatatat	tattaaa					377

&lt;210&gt; 94

&lt;211&gt; 495

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(495)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 94

ccctttgagg	ggtagggctc	cagttcccag	tggaagaaac	aggccaggag	aantgcgtgc	60
cgagctgang	cagatttccc	acagtgaacc	cagagccctg	ggctatagtc	tctgaccctt	120
ccaaggaaa	accaccttct	ggggacatgg	gctggagggc	aggacctaga	ggcaccaagg	180
gaaggcccca	ttccggggct	gttccccgag	gaggaaggga	aggggctctg	tgtgccqccc	240
acgaggaana	ggccctgant	cctgggatca	nacaccctt	cacgtgtatc	cccacacaaa	300
tgcaagctca	ccaaggtccc	ctctcagtc	cttccctaca	ccctgaacgg	ncactggccc	360
acaccacccc	agancancca	cccgccatgg	ggaatgtnt	caaggaatcg	cngggcaacg	420
tggaactctng	tcccnnaagg	gggcagaatc	tccaatagan	gganngaacc	cttgctnana	480
aaaaaaaaana	aaaaa					495

&lt;210&gt; 95

&lt;211&gt; 472

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(472)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 95

ggttacttgg	tttcattgcc	accacttagt	ggatgtcatt	tagaaccatt	ttgtctgctc	60
cctctggag	ccttgccgag	agcggacttt	gtaattgttg	gagaataact	gctgaatttt	120
tagctgtttt	gagttgattc	gcaccactgc	accacaactc	aatatgaaaa	ctatttnact	180
tatttattat	cttgtgaaaa	gtatacaatg	aaaattttgt	tcatactgta	tttatcaagt	240
atgatgaaaa	gcaatagata	tatattcttt	tattatgttn	aattatgatt	gccattatta	300
atcggcaaaa	tgtggagtgt	atgttctttt	cacagtaata	tatgcctttt	gtaacttcac	360
ttggttattt	tattgtaaat	gaattacaaa	attcttaatt	taagaaaatg	gtangttata	420
tttanttcan	taatttcttt	ccttgtttac	gttaattttg	aaaagaatgc	at	472

&lt;210&gt; 96

&lt;211&gt; 476

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(476)  
 <223> n = A,T,C or G

<400> 96  
 ctgaagcatt tcttcaaact tntctacttt tgtcattgat acctgtagta agttgacaat 60  
 gtgggtgaaat ttcaaaatta tatgtaactt ctactagttt tacttttctcc cccaagtctt 120  
 ttttaactca tgattttttac acacacaatc cagaacttat tatatagcct ctaagtcttt 180  
 attcttcaca gtagatgatg aaagagtcct ccagtgtctt gngcanaatg ttctagntat 240  
 agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat 300  
 tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct 360  
 gcaggctact ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt 420  
 tacaaagtct atcttcctca nangtctgtt aaggaacaat ttaatcttct agcttt 476

<210> 97  
 <211> 479  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(479)  
 <223> n = A,T,C or G

<400> 97  
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 aaataatgct gcaaaacttaa tgttcttatg caaaatggaa cgctaatagaa acacagctta 120  
 caatcgcaaa tcaaaaactca caagtgtccta tctgttgtag atttagtgta ataagactta 180  
 gattgtgctc cttoggatat gattgtttct canatcttgg gcaatnttcc ttagtcaaat 240  
 caggctacta gaattctggt attggatatn tgagagcatg aaatttttaa naatacactt 300  
 gtgattatna aattaatcac aaatttctact tatacctgct atcagcagct agaaaaacat 360  
 ntnnttttta natcaaagta ttttgtgttt ggaantgttn aaatgaaatc tgaatgtggg 420  
 ttcnatctta ttttttcccn gacnactant tnccttttta gggncctattc tganccatc 479

<210> 98  
 <211> 461  
 <212> DNA  
 <213> Homo sapien

<400> 98  
 agtgacttgt cctccaacaa aacccttga tcaagtttgh ggcaactgaca atcagaccta 60  
 tgctagttcc tgtcatctat tgcctactaa atgcagactg gaggggacca aaaaggggca 120  
 tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga 180  
 agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta 240  
 tgaagccact ctgaacacgc tggttatcta gatgagaaca gagaaataaa gtcagaaaaat 300  
 ttacctggag aaaagaggct ttggctgggg accatcccat tgaaccttct cttaaggact 360  
 ttaagaaaaa ctaccacatg ttgtgtatcc tgggtgccggc cgtttatgaa ctgaccaccc 420  
 tttggaataa tcttgacgct cctgaacttg ctctctgcg a 461

<210> 99  
 <211> 171  
 <212> DNA  
 <213> Homo sapien

<400> 99  
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 cggcgctct gcgggcccga ggaggagcgg ctggcggttg gggggagtgt gacccaccc 120

cggtgagaaa agccttctct agcgatctga gaggcgtgcc ttgggggtac c 171

<210> 100  
 <211> 269  
 <212> DNA  
 <213> Homo sapien

<400> 100  
 cgcccgcaag tgcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc 60  
 cgactgcgac gacggcgccg gcgacagtcg caggtgcagc gcggggcgct ggggtcttgc 120  
 aaggctgagc tgacgcgcga gaggtcgtgt cacgtccbac gaccttgacg ccgtcgggga 180  
 cagccggaac agagcccgtt gaagcgggag gcctcgggga gccctcggg aagggcggcc 240  
 cgagagatac gcaggtgcag gtggccgcc 269

<210> 101  
 <211> 405  
 <212> DNA  
 <213> Homo sapien

<400> 101  
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 gctagcaagg taacagggtta gggcatggtt acatgttcag gtcaacttcc ttgtcgtgg 120  
 ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaacgaagca aataacatgg 180  
 agtgggtgca ccctccctgt agaacctgtt tacaaagctt ggggcagttc acctggtctg 240  
 tgaccgtcat tttcttgaca tcaatgttat tagaagtcag gatattcttt agagagtcca 300  
 ctgttctgga gggagattag ggtttcttgc caaatccaac aaaatccact gaaaaagttg 360  
 gatgatcagt acgaataccg aggcattatc tcatatcgtt ggcca 405

<210> 102  
 <211> 470  
 <212> DNA  
 <213> Homo sapien

<400> 102  
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 ggcaacttaat ccatttttat ttcaaaatgt ctacaaattt aatcccatta tacggtattt 120  
 tcaaaatcta aattattcaa attagccaaa tccttaccaa ataataccca aaaatcaaaa 180  
 atatacttct ttcagcaaac ttgttacata aattaaanaa atatatacgg ctggtgtttt 240  
 caaagtacaa ttatcttaac actgcaaaac ttttaaggaa ctaaaataaa aaaaaacact 300  
 ccgcaaagg taaagggaac aacaaattct tttacaacac cattataaaa atcatatctc 360  
 aaatcttagg ggaatatata cttcacacgg gatcttaact tttactcact ttgtttattt 420  
 ttttaaacca ttgtttgggc ccaacacaat ggaatccccc ctggactagt 470

<210> 103  
 <211> 581  
 <212> DNA  
 <213> Homo sapien

<400> 103  
 tttttttttt ttttttttga cccccctctt ataaaaaaca agttaccatt ttatttttact 60  
 tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac 120  
 taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt 180  
 gaaaatcttc tctagctctt ttgactgtaa atttttgact cttgtaaaac atccaaattc 240  
 attttcttgg tctttaaaaa tatctaattc ttccattttt tccctattcc aagtcaattt 300  
 gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa 360  
 agggaaaaa ggaagagaaa tggcacacaa aacaaacatt ttatattcat atttctacct 420  
 acgttaataa aatagcattt tgtgaagcca gctcaaaaga aggcattagat ccttttatgt 480  
 ccatttttagt cactaaacga tatcaaagtg ccagaatgca aaaggtttgt gaacatttat 540

tcaaaagcta atataagata tttcacatac tcatctttct g

581

<210> 104  
<211> 578  
<212> DNA  
<213> Homo sapien

<400> 104  
 tttttttttt tttttttttt tttttctctt cttttttttt gaaatgagga tgcagttttt 60  
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 ctcttatgct atatcatatt ttaagttaaa ctaatgagtc actggcttat cttctcctga 180  
 aggaaatctg ttcattcttc tcattcatat agttatatca agtactacct tgcattatga 240  
 gaggtttttt ttctctattt acacatatat ttccatgtga atttgtatca aacctttatt 300  
 ttcattgcaaa ctagaaaata atgtttcttt tgcataagag aagagaacaa tatagcatta 360  
 caaaactgct caaattgttt gttaagttat ccattataat tagttggcag gagctaatac 420  
 aaatcacatt tacgacagca ataataaaac tgaagtacca gttaaatatc caaaataatt 480  
 aaaggaacat ttttagcctg ggtataatta gctaattcac tttacaagca tttattagaa 540  
 tgaattcaca tgttattatt cctagcccaa cacaatgg 578

<210> 105  
<211> 538  
<212> DNA  
<213> Homo sapien

<400> 105  
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 gaaaagtgcc ttacatttaa taaaagtttg tttctcaaag tgatcagagg aattagatat 120  
 gtcttgaaca ccaatattaa tttgaggaaa atacaccaa atacattaag taaattattt 180  
 aagatcatag agcttgtaag tgaaaagata aaatttgacc tcagaaactc tgagcattaa 240  
 aaatccacta tttagcaata aattactatg gacttcttgc ttttaatttg tgatgaatat 300  
 ggggtgtcac tggtaaacca acacattctg aaggatacat tacttagtga tagattctta 360  
 tgtactttgc taatacgtgg atatgagttg acaagtttct ctttcttcaa tcttttaagg 420  
 ggcgagaaat gaggaagaaa agaaaaggat tacgcatact gttctttcta tggaaggatt 480  
 agatatgttt cctttgccaa tattaaaaaa ataataatgt ttactactag tgaaaccc 538

<210> 106  
<211> 473  
<212> DNA  
<213> Homo sapien

<400> 106  
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 tttataaatg taagggtgcc ttattgagta atatattcct ccaagagtgg atgtgtccct 180  
 tctcccacca actaatgaac agcaacatta gtttaatttt attagtagat atacactgct 240  
 gcaaacgcta attctcttct ccatcccat gtgatattgt gtatatgtgt gagttggtag 300  
 aatgcatcac aatctacaat caacagcaag atgaagctag gctgggcttt cggtgaaaat 360  
 agactgtgtc tgtctgaatc aaatgatctg acctatcctc ggtggcaaga actcttcgaa 420  
 ccgcttcttc aaaggcgctg ccacatttgt ggctctttgc acttgtttca aaa 473

<210> 107  
<211> 1621  
<212> DNA  
<213> Homo sapien

<400> 107  
 cgccatggca ctgcaggga tctcggtcat ggagctgtcc ggcctggccc cgggcccgtt 60  
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ccgctacgac gtgagccgct tgggccgggg caagcgctcg ctagtgctgg acctgaagca 180
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cttccgccgc ggtgtcatgg agaaactcca gctgggcccā gagattctgc agcgggaaaa 300
tccaaggctt atttatgcca ggctgagtgg atttggccag tcaggaagct tctgccggtt 360
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cattgatgca aatatggtgg aaggaacagc atatttaagt tcttttctgt ggaaaactca 600
gaaatcgagt ctgtgggaag cacctcgagg acagaacatg ttggatggtg gagcaccttt 660
ctatacgact tacaggacag cagatgggga attcatggct gttggagcaa tagaacccca 720
gttctacgag ctgctgatca aaggacttgg actaaagctc gatgaacttc ccaatcagat 780
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ttttgaatgg gttctagtga aaaaggaatg atatattctt gaagacatcg atatacatTT 1500
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a

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<210> 108  
 <211> 382  
 <212> PRT  
 <213> Homo sapien

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<400> 108
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Gly Pro Phe Cys Ala Met Val Leu Ala Asp Phe Gly Ala Arg Val Val
20     25     30
Arg Val Asp Arg Pro Gly Ser Arg Tyr Asp Val Ser Arg Leu Gly Arg
35     40     45
Gly Lys Arg Ser Leu Val Leu Asp Leu Lys Gln Pro Arg Gly Ala Ala
50     55     60
Val Leu Arg Arg Leu Cys Lys Arg Ser Asp Val Leu Leu Glu Pro Phe
65     70     75     80
Arg Arg Gly Val Met Glu Lys Leu Gln Leu Gly Pro Glu Ile Leu Gln
85     90     95
Arg Glu Asn Pro Arg Leu Ile Tyr Ala Arg Leu Ser Gly Phe Gly Gln
100    105    110
Ser Gly Ser Phe Cys Arg Leu Ala Gly His Asp Ile Asn Tyr Leu Ala
115    120    125
Leu Ser Gly Val Leu Ser Lys Ile Gly Arg Ser Gly Glu Asn Pro Tyr
130    135    140
Ala Pro Leu Asn Leu Leu Ala Asp Phe Ala Gly Gly Gly Leu Met Cys
145    150    155    160
Ala Leu Gly Ile Ile Met Ala Leu Phe Asp Arg Thr Arg Thr Asp Lys
165    170    175
Gly Gln Val Ile Asp Ala Asn Met Val Glu Gly Thr Ala Tyr Leu Ser
180    185    190
Ser Phe Leu Trp Lys Thr Gln Lys Ser Ser Leu Trp Glu Ala Pro Arg

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195	200	205
Gly Gln Asn Met Leu Asp	Gly Gly Ala Pro Phe Tyr Thr Thr Tyr Arg	
210	215	220
Thr Ala Asp Gly Glu Phe Met Ala Val Gly Ala Ile Glu Pro Gln Phe		
225	230	235
Tyr Glu Leu Leu Ile Lys Gly Leu Gly Leu Lys Ser Asp Glu Leu Pro		
245	250	255
Asn Gln Met Ser Met Asp Asp Trp Pro Glu Met Lys Lys Lys Phe Ala		
260	265	270
Asp Val Phe Ala Lys Lys Thr Lys Ala Glu Trp Cys Gln Ile Phe Asp		
275	280	285
Gly Thr Asp Ala Cys Val Thr Pro Val Leu Thr Phe Glu Glu Val Val		
290	295	300
His His Asp His Asn Lys Glu Arg Gly Ser Phe Ile Thr Ser Glu Glu		
305	310	315
Gln Asp Val Ser Pro Arg Pro Ala Pro Leu Leu Leu Asn Thr Pro Ala		
325	330	335
Ile Pro Ser Phe Lys Arg Asp Pro Phe Ile Gly Glu His Thr Glu Glu		
340	345	350
Ile Leu Glu Glu Phe Gly Phe Ser Arg Glu Glu Ile Tyr Gln Leu Asn		
355	360	365
Ser Asp Lys Ile Ile Glu Ser Asn Lys Val Lys Ala Ser Leu		
370	375	380

&lt;210&gt; 109

&lt;211&gt; 1524

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 109

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gggcctggcc	atgcctcact	gagccagcgc	ctgcgcctct	acctcgccga	cagctggaac	120
cagtgcgacc	tagtggtct	cacctgcttc	ctcctgggcg	tgggctgccc	gctgacccc	180
ggtttgtagc	acctggggccg	cactgtcttc	tgcctcgact	tcatggtttt	cacggtgcgg	240
ctgcttcaca	tcttcacggt	caacaaacag	ctggggccca	agatcgatcat	cgtgagcaag	300
atgatgaagg	acgtgttctt	cttctctctt	ttcctcggcg	tgtggctggt	agcctatggc	360
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&lt;210&gt; 110

<211> 3410  
 <212> DNA  
 <213> Homo sapien

<400> 110

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<210> 111  
 <211> 1289  
 <212> DNA  
 <213> Homo sapien

<400> 111

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<210> 112  
 <211> 315  
 <212> PRT  
 <213> Homo sapien

<400> 112

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			20					25					30		
Phe	Phe	Leu	Phe	Phe	Leu	Gly	Val	Trp	Leu	Val	Ala	Tyr	Gly	Val	Ala
		35				40					45				
Thr	Glu	Gly	Leu	Leu	Arg	Pro	Arg	Asp	Ser	Asp	Phe	Pro	Ser	Ile	Leu
	50				55					60					
Arg	Arg	Val	Phe	Tyr	Arg	Pro	Tyr	Leu	Gln	Ile	Phe	Gly	Gln	Ile	Pro
	65			70					75					80	
Gln	Glu	Asp	Met	Asp	Val	Ala	Leu	Met	Glu	His	Ser	Asn	Cys	Ser	Ser
		85						90					95		
Glu	Pro	Gly	Phe	Trp	Ala	His	Pro	Pro	Gly	Ala	Gln	Ala	Gly	Thr	Cys
	100						105					110			
Val	Ser	Gln	Tyr	Ala	Asn	Trp	Leu	Val	Val	Leu	Leu	Leu	Val	Ile	Phe
	115				120						125				
Leu	Leu	Val	Ala	Asn	Ile	Leu	Leu	Val	Asn	Leu	Leu	Ile	Ala	Met	Phe
	130				135						140				



Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu Tyr Trp Lys  
 145 150 155 160  
 Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg Pro Ala Leu  
 165 170 175  
 Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Leu Arg Gln  
 180 185 190  
 Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu  
 195 200 205  
 His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr  
 210 215 220  
 Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp  
 225 230 235 240  
 Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val  
 245 250 255  
 Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg  
 260 265 270  
 Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly  
 275 280 285  
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 Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp  
 305 310 315

<210> 113  
 <211> 553  
 <212> PRT  
 <213> Homo sapien

<400> 113  
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 20 25 30  
 Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val  
 35 40 45  
 Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly  
 50 55 60  
 Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly  
 65 70 75 80  
 Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile  
 85 90 95  
 Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu  
 100 105 110  
 Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly  
 115 120 125  
 Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu  
 130 135 140  
 Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala  
 145 150 155 160  
 Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr  
 165 170 175  
 Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu  
 180 185 190  
 Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu  
 195 200 205  
 Thr Cys Val Ala Ala Thr Leu Val Ala Glu Glu Ala Ala Leu Gly  
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 Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His

[illegible]

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<210> 114
<211> 241
<212> PRT
<213> Homo sapien
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<400> 114															
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Leu	Ile	Phe	Leu	Cys	Gly	Ala	Ala	Leu	Leu	Ala	Val	Gly	Ile	Trp	Val
			20					25					30		
Ser	Ile	Asp	Gly	Ala	Ser	Phe	Leu	Lys	Ile	Phe	Gly	Pro	Leu	Ser	Ser
		35					40					45			
Ser	Ala	Met	Gln	Phe	Val	Asn	Val	Gly	Tyr	Phe	Leu	Ile	Ala	Ala	Gly
	50					55					60				
Val	Val	Val	Phe	Ala	Leu	Gly	Phe	Leu	Gly	Cys	Tyr	Gly	Ala	Lys	Thr
65					70					75					80

Glu	Ser	Lys	Cys	Ala	Leu	Val	Thr	Ph	Phe	Phe	Ile	Leu	Leu	Leu	Ile
				85					90					95	
Phe	Ile	Ala	Glu	Val	Ala	Ala	Ala	Val	Val	Ala	Leu	Val	Tyr	Thr	Thr
		100						105					110		
Met	Ala	Glu	His	Phe	Leu	Thr	Leu	Leu	Val	Val	Pro	Ala	Ile	Lys	Lys
		115					120					125			
Asp	Tyr	Gly	Ser	Gln	Glu	Asp	Phe	Thr	Gln	Val	Trp	Asn	Thr	Thr	Met
	130					135					140				
Lys	Gly	Leu	Lys	Cys	Cys	Gly	Phe	Thr	Asn	Tyr	Thr	Asp	Phe	Glu	Asp
145					150					155					160
Ser	Pro	Tyr	Phe	Lys	Glu	Asn	Ser	Ala	Phe	Pro	Pro	Phe	Cys	Cys	Asn
				165					170					175	
Asp	Asn	Val	Thr	Asn	Thr	Ala	Asn	Glu	Thr	Cys	Thr	Lys	Gln	Lys	Ala
		180						185					190		
His	Asp	Gln	Lys	Val	Glu	Gly	Cys	Phe	Asn	Gln	Leu	Leu	Tyr	Asp	Ile
	195						200						205		
Arg	Thr	Asn	Ala	Val	Thr	Val	Gly	Gly	Val	Ala	Ala	Gly	Ile	Gly	Gly
	210					215					220				
Leu	Glu	Leu	Ala	Ala	Met	Ile	Val	Ser	Met	Tyr	Leu	Tyr	Cys	Asn	Leu
225					230					235					240
Gln															

&lt;210&gt; 115

&lt;211&gt; 366

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 115

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ttagtc						366

&lt;210&gt; 116

&lt;211&gt; 282

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(282)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 116

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agactttact	attttcatat	tttaagacac	atgattttatc	ctatttttagt	aacctgggtc	180
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&lt;210&gt; 117

&lt;211&gt; 305

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<220>  
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 <222> (1)...(305)  
 <223> n = A,T,C or G

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 aataaggcaa aatatatgaa acaacagggtc tcgagatatt ggaaatcagt caatgaagga 180  
 tactgatccc tgatcactgt cctaattgcag gatgtgggaa acagatgagg tcacctctgt 240  
 gactgccccca gottactgcc tgtagagagt ttctangctg cagttcagac agggagaaat 300  
 tgggt 305

<210> 118  
 <211> 71  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(71)  
 <223> n = A,T,C or G

<400> 118  
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 aantcctggg t 71

<210> 119  
 <211> 212  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(212)  
 <223> n = A,T,C or G

<400> 119  
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 agtaagctgg cccttctaataaaaagaaaat tgaaagggtt ctcactaanc ggaattaant 180  
 aatggantca aganactccc aggcctcagc gt 212

<210> 120  
 <211> 90  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(90)  
 <223> n = A,T,C or G

<400> 120  
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<210> 121  
 <211> 218  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(218)  
 <223> n = A,T,C or G

<400> 121  
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 gaataagatt tgctaaaaga ttgggggcta aaacatgggt attgggagac atttctgaag 120  
 atatncangt aaattangga atgaattcat gggtcttttg ggaattcctt tacgatngcc 180  
 agcatanact tcatgtgggg atancagcta cccttgta 218

<210> 122  
 <211> 171  
 <212> DNA  
 <213> Homo sapien

<400> 122  
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 caccaccccg gcgggggtcat ctgtgccaca ggtccctgtt gacagtgcgg t 171

<210> 123  
 <211> 76  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(76)  
 <223> n = A,T,C or G

<400> 123  
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 ttatcaanta ttgtgt 76

<210> 124  
 <211> 131  
 <212> DNA  
 <213> Homo sapien

<400> 124  
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 ttaagatttg t 131

<210> 125  
 <211> 432  
 <212> DNA  
 <213> Homo sapien

<400> 125  
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ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgctgaagat	180
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ctcttgaagt atcagtcact tttagaatg tttcttagtt actgcatact tcatggatcc	300
catggtgggg gtcttgcac tgtaagaatg gaattgattt tgcttttgca agaattctcag	360
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<210> 126  
 <211> 112  
 <212> DNA  
 <213> Homo sapien

<400> 126	
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agtaagaatg atatttcccc ccagggatca ccaaatttt ataaaaattt gt	112

<210> 127  
 <211> 54  
 <212> DNA  
 <213> Homo sapien

<400> 127	
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<210> 128  
 <211> 323  
 <212> DNA  
 <213> Homo sapien

<400> 128	
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctccct ctaccagctc	60
acctgagata acagaatgaa aatggaagga cagccagatt totcctttgc totctgctca	120
ttctctctga agtctaggtt acccattttg gggaccatt ataggcaata aacacagtgc	180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttcctttt tottagcctt	240
ttctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct	300
aggctgcctt cttttccatg tcc	323

<210> 129  
 <211> 192  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(192)  
 <223> n = A,T,C or G

<400> 129	
acatacatgt gtgtatattt ttaaataatca cttttgtatc actctgactt tttagcatatc	60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc	120
tagcacattc atctgtgata naaagatagg tgagtttcat ttcttccacg ttggccaatg	180
gataaacaaa gt	192

<210> 130  
 <211> 362  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(362)  
 <223> n = A,T,C or G

<400> 130  
 ccctttttta tggaatgagt agactgtatg ttggaanatt tanccacaac ctcttttgaca 60  
 tataatgacg caacaaaaag gtgctgttta gtcctatggt tcagtttatg cccctgacaa 120  
 gtttccattg tgttttgccg atcttctggc taatcgtggt atcctccatg ttattagtaa 180  
 ttctgtattc cattttgtta acgcctggta gatgtaacct gctangaggc taactttata 240  
 cttatttaaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat 300  
 tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaatttta aaaagtaatg 360  
 gg 362

<210> 131  
 <211> 332  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(332)  
 <223> n = A,T,C or G

<400> 131  
 ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca 60  
 gtangactgg tatgggttgc gctgtccaga taaaaacatt tgaagagctc caaaatgaga 120  
 gttctccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc 180  
 ttctgaacta gattaaggca gcttgtaa atctgatgtat ttggtttatt atccaactaa 240  
 cttccatctg ttatcactgg agaaagccca gactcccan gacnggtacg gattgtgggc 300  
 atanaaggat tgggtgaagc tggcgttgtg gt 332

<210> 132  
 <211> 322  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(322)  
 <223> n = A,T,C or G

<400> 132  
 actttttgcca ttttgtatat ataaacaatc ttgggacatt ctctgaaaa ctaggtgtcc 60  
 agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat 120  
 ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggaccttg tatctcgggt 180  
 tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg 240  
 ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct aggggaagcct 300  
 gtaacaatct acaattggtc ca 322

<210> 133  
 <211> 278  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(278)

<223> n = A,T,C or G

<400> 133

acaagccttc	acaagtttaa	ctaaattggg	attaatcttt	ctgtanttat	ctgcataatt	60
cttggttttc	tttccatctg	gctcctgggt	tgacaatttg	tggaacaac	tctattgcta	120
ctatttaaaa	aaaatcacaa	atctttccct	ttaagctatg	ttnaattcaa	actattcctg	180
ctattcctgt	tttgtcaaag	aaattatatt	tttcaaaata	tgtntatttg	tttgatgggt	240
cccacgaac	actaataaaa	accacagaga	ccagcctg			278

<210> 134

<211> 121

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(121)

<223> n = A,T,C or G

<400> 134

gtttanaaaa	cttgtttagc	tccatagagg	aaagaatggt	aaactttgta	ttttaaaaca	60
tgattctctg	aggttaaact	tggttttcaa	atgttatatt	tacttgtatt	ttgcttttgg	120
t						121

<210> 135

<211> 350

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(350)

<223> n = A,T,C or G

<400> 135

acttanaacc	atgcctagca	catcagaatc	cctcaaagaa	catcagtata	atcctataacc	60
atancaagtg	gtgactgggt	aagcgtgcga	caaagggtcag	ctggcacatt	acttgtgtgc	120
aaacttgata	cttttgttct	aagtaggaac	tagtatacag	tnccctaggan	tggtactcca	180
gggtgcccc	caactcctgc	agccgctcct	ctgtgccagn	ccctgnaagg	aactttcgct	240
ccacctcaat	caagccctgg	gccatgctac	ctgcaattgg	ctgaacaaac	gtttgctgag	300
ttcccaagga	tgcaaagcct	gggtgctcaac	tcctggggcg	tcaactcagt		350

<210> 136

<211> 399

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(399)

<223> n = A,T,C or G

<400> 136

tgtaccgtga	agacgacaga	agttgcatgg	cagggacagg	gcagggccga	ggccagggtt	60
gctgtgattg	tatccgaata	ntcctcgtga	gaaaagataa	tgagatgacg	tgagcagcct	120
gcagacttgt	gtctgccttc	aanaagccag	acaggaaggc	cctgcctgcc	ttggetctga	180
cctggcgggc	agccagccag	ccacaggtgg	gcttccttct	tttgtggtga	caacnccaag	240
aaaactgcag	aggcccaggg	tcaggtgtna	gtgggtangt	gaccataaaa	caccaggtgc	300



tcccaggaac ccgggcaaag gccatcccca cctacagcca gcatgcccac tggcgtgatg 360  
 ggtgcagang gatgaagcag ccagntgttc tgctgtggt 399

<210> 137  
 <211> 165  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(165)  
 <223> n = A,T,C or G

<400> 137  
 actggtgtgg tngggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt 60  
 ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga 120  
 ttggtgtgtc ccaactggtg tcactgtcat tgggtggggt cctgt 165

<210> 138  
 <211> 338  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(338)  
 <223> n = A,T,C or G

<400> 138  
 actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc 60  
 ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgoccaa 120  
 tgctgggcag tctcccatgc cttccacagt gaaagggtt gagaaaaatc acatccaatg 180  
 tcatgtgttt ccagccacac caaaagggtc ttgggggtgga gggctggggg catananggt 240  
 cangcctcag gaagcctcaa gttccattca gctttgccac tgtacattcc ccatntttaa 300  
 aaaaactgat gccttttttt tttttttttg taaaattc 338

<210> 139  
 <211> 382  
 <212> DNA  
 <213> Homo sapien

<400> 139  
 gggaatcttg gtttttggca tctggtttgc ctatagccga ggccactttg acagaacaaa 60  
 gaaagggact tcgagtaaga aggtgattta cagccagcct agtgcccga gtgaaggaga 120  
 attcaaacag acctcgtcat tcttggtgtg agcctggctg gctcaccgcc tatcatctgc 180  
 atttgctta ctcaggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg 240  
 ccttatttgt cttctacacc ccacagggcc cctacttct tcggatgtgt ttttaataat 300  
 gtcagctatg tgccccatcc tccttcatgc cctccctccc tttcctacca ctgctgagt 360  
 gcctggaact tgttttaaagt gt 382

<210> 140  
 <211> 200  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(200)

<223> n = A,T,C or G

<400> 140

acccaaanctt	ctttctgttg	tgttngattt	tactataggg	gtttngcttn	ttctaaanat	60
acttttcatt	taacancttt	tgtaaagtgt	caggctgcac	tttgcctcat	anaattattg	120
ttttcacatt	tcaacttgta	tgtgtttgtc	tcttanagca	ttggtgaaat	cacatatttt	180
atattcagca	taaaggagaa					200

<210> 141

<211> 335

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(335)

<223> n = A,T,C or G

<400> 141

actttatttt	caaaacactc	atatgttgca	aaaaacacat	agaaaaataa	agtttggtgg	60
gggtgctgac	taaacttcaa	gtcacagact	tttatgtgac	agattggagc	agggtttggt	120
atgcatgtag	agaaccctaa	ctaattttatt	aaacaggata	gaaacaggct	gtctgggtga	180
aatggttctg	agaaccatcc	aattcacctg	tcagatgctg	atanactagc	tcttcagatg	240
tttttctacc	agttcagaga	tnggttaatg	actantttca	atggggaaaa	agcaagatgg	300
attcacaaac	caagtaattt	taaacaaaga	cactt			335

<210> 142

<211> 459

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(459)

<223> n = A,T,C or G

<400> 142

accagggttaa	tattgccaca	tatatccttt	ccaattgcgg	gctaaacaga	cgtgtattta	60
gggttggttta	aagacaaccc	agcttaatat	caagagaaat	tgtgaccttt	catggagtat	120
ctgatggaga	aaacactgag	ttttgacaaa	tcttatttta	ttcagatagc	agtctgatca	180
cacatgggtcc	aacaacactc	aaataataaa	tcaaataatna	tcagatgtta	aagattggtc	240
ttcaaacatc	atagccaatg	atgcccgcgt	tgcctataat	ctctccgaca	taaaaccaca	300
tcaacacctc	agtggccacc	aaaccattca	gcacagcttc	cttaactgtg	agctgtttga	360
agctaccagt	ctgagcacta	ttgactatnt	ttttcangct	ctgaatagct	ctagggatct	420
cagcangggg	gggaggaacc	agctcaacct	tggcggtant			459

<210> 143

<211> 140

<212> DNA

<213> Homo sapien

<400> 143

acatttcctt	ccaccaagtc	aggactcctg	gcttctgtgg	gagttcttat	cacctgaggg	60
aatccaaac	agtctctcct	agaaaggaat	agtgtcacca	acccacacca	tctccctgag	120
accatccgac	ttccctgtgt					140

<210> 144

<211> 164

<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(164)  
 <223> n = A,T,C or G

<400> 144  
 acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct 60  
 atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaaatttg 120  
 aggcaattaa tccatatttg ttttcaataa ggaaaaaaag atgt 164

<210> 145  
 <211> 303  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(303)  
 <223> n = A,T,C or G

<400> 145  
 acgtagacca tccaactttg tatttghtaat ggcaaacatc cagnagcaat tcctaaacaa 60  
 actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat 120  
 gcaggacagc tatcataagt cggcccaggc atccagatac taccatttgt ataaacttca 180  
 gtaggggagt ccatccaagt gacagggtcta atcaaaggag gaaatggaac ataagcccag 240  
 tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat 300  
 caa 303

<210> 146  
 <211> 327  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(327)  
 <223> n = A,T,C or G

<400> 146  
 actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac 60  
 actggcctgg agtgactcat tgctctggtt ggttgagaga gtcctttgc caacaggcct 120  
 ccaagtcagg gctgggattt gtttccttcc cacattctag caacaatatg ctggccactt 180  
 cctgaacagg gaggggtggga ggagccagca tggaacaagc tgccacttcc taaagtagcc 240  
 agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg 300  
 taggggtgag ctgtgtgact ctatggt 327

<210> 147  
 <211> 173  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(173)  
 <223> n = A,T,C or G

<400> 147  
 acattgtttt tttagataa agcattgana gagctctcct taaogtgaca caatggaagg 60  
 actggaacac ataccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt 120  
 atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt 173

<210> 148  
 <211> 477  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(477)  
 <223> n = A,T,C or G

<400> 148  
 acaaccactt tatctcatcg aattttttaac ccaaactcac tcaactgtgcc tttctatcct 60  
 atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcactact 120  
 gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg 180  
 gtggtcctag tggccatcag tccangcctg caccttgagc ccttgagctc cattgctcac 240  
 nccanccac ctacccgacc ccatcctctt acacagctac ctccctgtct tctaacccca 300  
 tagattatnt ccaaattcag tcaattaagt tactattaac actctaccgg acatgtccag 360  
 caccactggt aagccttctc cagccaacac acacacacac acacncacac acacacatat 420  
 ccaggcacag gctacctcat cttcacaatc acccctttaa ttaccatgct atggtgg 477

<210> 149  
 <211> 207  
 <212> DNA  
 <213> Homo sapien

<400> 149  
 acagttgtat tataatatca agaaataaac ttgcaatgag agcattttaag agggaagaac 60  
 taacgtatatt tagagagcca aggaagggtt ctgtggggag tgggatgtaa ggtggggcct 120  
 gatgataaat aagagtcagc caggttaagt ggtggtgtgg tatgggcaca gtgaagaaca 180  
 ttccaggcag agggaacagc agtgaaa 207

<210> 150  
 <211> 111  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(111)  
 <223> n = A,T,C or G

<400> 150  
 acottgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg 60  
 cacttaaagt tggtcagtgt ttggacttgt taactantgg catctttggg t 111

<210> 151  
 <211> 196  
 <212> DNA  
 <213> Homo sapien

<400> 151  
 agcgcggcag gtcattatga acattccaga tacctatcat tactcgatgc tgttgataac 60

agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaacccat	120
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggccccac tgtctacgag	180
gtgcatccgg ctgagt	196

<210> 152  
 <211> 132  
 <212> DNA  
 <213> Homo sapien

<400> 152	
acagcacttt cacatgtaag aagggagaaa ttcttaaagt taggagaaag ataacagAAC	60
cttccccttt tcatctagt gtggaaacct gatgctttat gttgacagga atagaaccag	120
gagggagttt gt	132

<210> 153  
 <211> 285  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(285)  
 <223> n = A,T,C or G

<400> 153	
acaanaccCa nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag	60
cttctgtctt tatgtcctca tctgacaact ctttaccatt tttatcctcg ctgagcagga	120
gcacatcaat aaagtccaaa gtcttggaact tggccttggc ttggaggaag tcatcaaac	180
cctggctagt gaggggtgcg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca	240
gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt	285

<210> 154  
 <211> 333  
 <212> DNA  
 <213> Homo sapien

<400> 154	
accacagtcc tgttggggcca gggcttcagt accctttctg tgaaaagcca tattatcacc	60
accccaaatt ttctcttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac	120
cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgctgcctg	180
attggcacag gagtcgaagg tgttcagctc ccctcctccg tggaacgaga ctctgatttg	240
agtttcacaa attctcgggc cacctcgtca ttgctcctct gaaataaaat cgggagaatg	300
gtcaggcctg tctcatccat atggatcttc cgg	333

<210> 155  
 <211> 308  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(308)  
 <223> n = A,T,C or G

<400> 155	
actggaaata ataaaaccca catcacagt ttgtgtcaaa gatcatcagg gcatggatgg	60
gaaagtgtt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat	120
ttgaatcacg gtgcatacaa actctcctgc ctgctcctcc tgggccccag cccagcccc	180

atcacagctc actgctctgt tcatccaggc ccagcatgta gtggctgatt cttcttggt 240  
 gcttttagcc tccanaagtt tctctgaagc ca'accaaacc tctangtgta aggcattgctg 300  
 gccctggt 308

<210> 156  
 <211> 295  
 <212> DNA  
 <213> Homo sapien

<400> 156  
 accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta 60  
 ttattgatta ctgagagaac tgtagacat ttagttgaag attttctaca caggaactga 120  
 gaataggaga ttatgtttgg cctcatatt ctctcctatc ctccttgctt cattctatgt 180  
 ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat 240  
 aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat 295

<210> 157  
 <211> 126  
 <212> DNA  
 <213> Homo sapien

<400> 157  
 acaagtttaa atagtgtgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct 60  
 gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc 120  
 cttagt 126

<210> 158  
 <211> 442  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(442)  
 <223> n = A,T,C or G

<400> 158  
 acccaactggt cttggaaaca cccatcctta atacgatgat ttttctgtcg tgtgaaaatg 60  
 aancagcag gctgccccta gtcagtcctt ccttcagag aaaaagagat ttgagaaagt 120  
 gcctgggtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatat 180  
 ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta 240  
 natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtgg 300  
 ccaaccctgt tttcccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga 360  
 nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg 420  
 tgttcattct ctgatgtcct gt 442

<210> 159  
 <211> 498  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(498)  
 <223> n = A,T,C or G

<400> 159  
 acttcaggt aacgttggtg tttccgttga gcctgaactg atgggtgacg ttgtaggttc 60

tccaacaaga	actgaggttg	cagagcgggt	aggggaagagt	gctgttccag	ttgcacctgg	120
gctgctgtgg	actgttggtg	attcctcact	acggcccaag	gttgtggaac	tgccanaaag	180
gtgtgttggt	gganttgagc	tcgggcggct	gtggtaggtt	gtgggctctt	caacaggggc	240
tgctgtgggt	ccgggangtg	aangtggttg	gtcacttgag	cttggccagc	tctggaaagt	300
antanattct	tcctgaaggc	cagcgcttgt	ggagctggca	ngggtcantg	ttgtgtgtaa	360
cgaaccagt	ctgctgtggg	tgggtgtana	tcctccacaa	agcctgaagt	tatggtgtcn	420
tcaggtaana	atgtggttcc	agtgtccctg	ggcngctgtg	gaagggtgta	nattgtcacc	480
aagggaataa	gctgtggt					498

&lt;210&gt; 160

&lt;211&gt; 380

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(380)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 160

acctgcatcc	agcttccctg	ccaaactcac	aaggagacat	caacctctag	acagggaaac	60
agcttcagga	tacttccagg	agacagagcc	accagcagca	aaacaaatat	tcccatgcct	120
ggagcatggc	atagaggaag	ctganaaatg	tggggtctga	ggaagccatt	tgagtctggc	180
cactagacat	ctcatcagcc	acttgtgtga	agagatgccc	catgacccca	gatgcctctc	240
ccacccttac	ctccatctca	cacacttgag	ctttccactc	tgtataattc	taacatcctg	300
gagaaaaatg	gcagtttgac	cgaacctgtt	cacaacggtg	gaggctgatt	tctaacgaaa	360
cttgtagaat	gaagcctgga					380

&lt;210&gt; 161

&lt;211&gt; 114

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 161

actccacatc	ccctctgagc	aggcgggttg	cgttcaaggt	gtatttggcc	ttgcctgtca	60
cactgtccac	tggcccctta	tccacttggt	gcttaatccc	tcgaaagagc	atgt	114

&lt;210&gt; 162

&lt;211&gt; 177

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 162

actttctgaa	tcgaatcaaa	tgatacttag	tgtagtttta	atatcctcat	atatatcaaa	60
gttttactac	tctgataatt	ttgtaaacca	ggttaaccaga	acatccagtc	atacagttt	120
tggtgatata	taacttggca	ataacccagt	ctggtgatac	ataaaactac	tcactgt	177

&lt;210&gt; 163

&lt;211&gt; 137

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(137)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 163

catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtgac 60  
 canagaagge agctacggct actcctacat cctggcgtgg gtggccttcg cctgcacctt 120  
 catcagcgge atgatgt 137

<210> 164  
 <211> 469  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(469)  
 <223> n = A,T,C or G

<400> 164  
 cttatcacia tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta 60  
 tgcaatgcat catgctatct catacctaata gagggagttc caggagattc aaccaggaaa 120  
 tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt 180  
 gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg 240  
 ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg 300  
 gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct 360  
 tctagtaggc acagggtcc caggccaggc ctcattctcc tctggcctct aatagtcaat 420  
 gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt 469

<210> 165  
 <211> 195  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(195)  
 <223> n = A,T,C or G

<400> 165  
 acagttttttt atanatatcg acattgcggg cacttgtggt cagtttcata aagctgggtgg 60  
 atccgctgtc atccactatt ccttggctag agtaaaaatt attcttatag cccatgtccc 120  
 tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact 180  
 tcctctgaga tgagt 195

<210> 166  
 <211> 383  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(383)  
 <223> n = A,T,C or G

<400> 166  
 acatcttagt agtgtggcac atcagggggc catcagggtc acagtcactc atagcctcgc 60  
 cgaggtcgga gtccacacca ccggtgtagg tgtgctcaat cttgggcttg gcgcccacct 120  
 ttggagaagg gatatgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt 180  
 tttgcagacc agcctgagca aggggcggat gttcagcttc agtcctcct tcgtcagggtg 240  
 gatgccaacc tcgtctangg tccgtgggaa gctgggtgct acntcaccta caacctgggc 300  
 gangatctta taaagaggct ccnagataaa ctccacgaaa cttctctggg agctgctagt 360  
 nggggccttt ttggtgaact ttc 383



<210> 167  
 <211> 247  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(247)  
 <223> n = A,T,C or G

<400> 167  
 acagagccag accttggcca taaatgaanc agagattaag actaaacccc aagtcganat 60  
 tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc 120  
 tatanccata cacagagcca actctcaggc caaggcnatg gttggggcag anccagagac 180  
 tcaatctgan tccaaagtgg tggttggaac actggtcatg acanaggcag tgactctgac 240  
 tgangtc 247

<210> 168  
 <211> 273  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(273)  
 <223> n = A,T,C or G

<400> 168  
 acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa 60  
 aatccctcan ccttggtctt cactactgtc tatactgana gtgtcatgtt tccacaaagg 120  
 gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag taggggtgggc 180  
 aattcccaac ttccttgcca caagcttccc aggcctttctc ccctggaaaa ctccagcttg 240  
 agtcccagat acactcatgg gctgccttgg gca 273

<210> 169  
 <211> 431  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(431)  
 <223> n = A,T,C or G

<400> 169  
 acagccttgg cttccccaaa ctccacagtc tcagtgcaga aagatcatct tccagcagtc 60  
 agctcagacc aggggtcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta 120  
 ctactgtcaa atgaccccc atacttcctc aaaggctgtg gtaagttttg cacagggtgag 180  
 ggcagcagaa aggggggtant tactgatgga caccatcttc tctgtatact ccacactgac 240  
 cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcaactgctgg gcaccagctc 300  
 acgcacatca ctgacaaccg ggatggaaaa agaantgcc aactttcatac atccaactgg 360  
 aaagtgatct gatactggat tcttaattac cttcaaaagc ttctgggggc catcagctgc 420  
 tcgaacactg a 431

<210> 170  
 <211> 266  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(266)

<223> n = A,T,C or G

<400> 170

acctgtgggc	tggtgtgta	tgctgtgcc	ggctgtgaa	agggagtca	gaggtggagc	60
tcaaggagct	ctgcaggcat	tttgccaanc	ctctccanag	canagggagc	aacctacact	120
ccccgctaga	aagacaccag	attggagtcc	tgggaggggg	agttgggggtg	ggcatttgat	180
gtatacttgt	cacctgaatg	aangagccag	agaggaanga	gacgaanatg	anattggcct	240
tcaaagctag	gggtctggca	ggtgga				266

<210> 171

<211> 1248

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1248)

<223> n = A,T,C or G

<400> 171

ggcagccaaa	tcataaacgg	cgaggactgc	agcccgcact	cgcagccctg	gcaggcggca	60
ctggatcatg	aaaacgaatt	gttctgtctg	ggcgtcctgg	tgcatccgca	gtgggtgctg	120
tcagccgcac	actgtttcca	gaagtgagt	cagagctcct	acaccatcgg	gctgggcctg	180
cacagtcttg	aggccgacca	agagccagg	agccagatgg	tggaggccag	cctctccgta	240
cggcaccag	agtacaacag	acccttgctc	gctaacgacc	tcagtctcat	caagttggac	300
gaatccgtgt	ccgagtctga	caccatccgg	agcatcagca	ttgottcgca	gtgccctacc	360
gcggggaaact	cttgctctgt	ttctggctgg	ggtctgtctg	ogaacggcag	aatgcctacc	420
gtgctgcagt	gcgtgaacgt	gtcgggtggt	tctgaggagg	tctgcagtaa	gctctatgac	480
ccgctgtacc	accccagcat	gttctgcgcc	ggcggagggg	aagaccagaa	ggactcctgc	540
aacggtgact	ctggggggcc	cctgatctgc	aacgggtact	tgacgggcct	tgtgtctttc	600
ggaaaagccc	cgtgtggcca	agttggcgtg	ccagggtgtct	acaccaacct	ctgcaaattc	660
actgagtggg	tagagaaaac	cgtccaggcc	agtttaactct	ggggactggg	aacccatgaa	720
attgaccccc	aaatacatcc	tgcggaagga	attcagggaat	atctgttccc	agccccctct	780
ccctcaggcc	caggagtcca	ggccccagc	ccctctctcc	tcaaaccaag	ggtacagatc	840
cccagccctc	cctccctcag	acccaggagt	ccagaccccc	cagccccctc	tccctcagac	900
ccaggagtcc	agccccctct	ccctcagacc	caggagtcca	gacccccag	cccctcctcc	960
ctcagaccca	gggttcagg	cccccaaccc	ctctccctc	agactcagag	gtccaagccc	1020
ccaaccntc	attccccaga	cccagagggtc	cagggtcccag	cccctcntcc	ctcagaccca	1080
gcggtccaat	gccacctaga	ctntccctgt	acacagtgcc	cccttggtggc	acgttgaccc	1140
aaccttacca	gttggttttt	catttttngt	ccctttcccc	tagatccaga	aataaagttt	1200
aagagaagng	caaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaa		1248

<210> 172

<211> 159

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(159)

<223> Xaa = Any Amino Acid

<400> 172

Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro  
 1 5 10 15  
 Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser  
 20 25 30  
 Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr  
 35 40 45  
 Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly  
 50 55 60  
 Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu  
 65 70 75 80  
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe  
 85 90 95  
 Cys Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser  
 100 105 110  
 Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe  
 115 120 125  
 Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn  
 130 135 140  
 Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser  
 145 150 155

<210> 173  
 <211> 1265  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(1265)  
 <223> n = A,T,C or G

<400> 173  
 ggcagcccgc actcgagccc ctggcaggcg geactgggtca tggaaaaacga attgttctgc 60  
 tcgggcgctcc tgggtgcatcc gcagtgggtg ctgtcagccg cacactgttt ccagaactcc 120  
 tacaccatcg ggctgggccc gcacagtctt gaggccgacc aagagccagg gagccagatg 180  
 gtggaggcca gcctctccgt acggcaccca gactacaaca gaccttgct cgctaacgac 240  
 ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc 300  
 attgcttcgc agtgccctac cgcggggaac tcttgctctg tttctggctg ggggtctgctg 360  
 gcgaacggtg agctcacggg tgtgtgtctg cctcttcaa ggaggtctc tgcccagtcg 420  
 cgggggctga cccagagctc tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga 480  
 acgtgtcggg ggtgtctgag gaggtctgca gtaagctcta tgaccgctg taccacccca 540  
 gcatgttctg cgccggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg 600  
 ggcccctgat ctgcaacggg tacttgagg gccttggtc tttcgaaaa gccccgtgtg 660  
 gccaaagtgg cgtgccagggt gtctacacca acctctgcaa attcactgag tggatagaga 720  
 aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac 780  
 atcctgcgga aggaattcag gaatatctgt tcccagcccc tcttccctca ggcccaggag 840  
 tccaggcccc cagcccctcc tccctcaaac caagggtaca gatccccagc cctcctccc 900  
 tcagaccag gagtccagac cccccagccc ctctcctc agaccagga gtccagcccc 960  
 tctcctntca gaccaggag tccagacccc ccagcccctc ctccctcaga cccaggggtt 1020  
 gagggcccca acccctcctc cttcagagtc agaggtccaa gcccacaacc cctcgttccc 1080  
 cagaccaga ggtnnagggt ccagcccctc ttcctcaga cccagnggtc caatgccacc 1140  
 tagattttcc ctgnacacag tgcccccttg tggngngttg acccaacctt accagttggg 1200  
 ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa 1260  
 aaaaa 1265

<210> 174  
 <211> 1459  
 <212> DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(1459)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 174

ggtcagccgc	acactgtttc	cagaagtgcg	tgcagagctc	ctacaccatc	gggctggggc	60
tgcacagtct	tgaggccgac	caagagccag	ggagccagat	ggtggaggcc	agcctctccg	120
tacggcacc	agagtacaac	agacccttgc	tcgctaacga	cctcatgctc	atcaagttgg	180
acgaatccgt	gtccgagttc	gacaccatcc	ggagcatcag	cattgcttcg	cagtgcctta	240
ccgcggggaa	ctcttgccctc	gtttctggct	ggggtctgct	ggcgaacggg	gagctcacgg	300
gtgtgtgtct	gccctcttca	aggaggtcct	ctgcccagtc	gcgggggctg	acccagagct	360
ctgcgtccca	ggcagaatgc	ctaccgtgct	gcagtgcgtg	aacgtgtcgg	tggtgtctga	420
ngaggtctgc	antaagctct	atgaccctgc	gtaccacccc	ancatgttct	gcgcccggcg	480
agggcaagac	cagaaggact	cctgcaacgt	gagagagggg	aaaggggagg	gcaggcgact	540
caggggaagg	tgagaaagg	ggagacagag	acacacaggg	ccgcatggcg	agatgcagag	600
atggagagac	acacagggag	acagtgcaca	ctagagagag	aaactgagag	aaacagagaa	660
ataaacacag	gaataaagag	aagcaaagga	agagagaaac	agaaacagac	atggggaggc	720
agaaacacac	acacatagaa	atgcagttga	ccttccaaca	gcatggggcc	tgagggcggg	780
gacctccacc	caatagaaaa	tcctcttata	acttttgact	ccccaaaaac	ctgactagaa	840
atagcctact	gttgacgggg	agccttacca	ataacataaa	tagtcgattt	atgcatacgt	900
tttatgcatt	catgatatac	ctttgttgga	attttttgat	atttctaagc	tacacagttc	960
gtctgtgaat	tttttttaaat	tggtgcaact	ctcctaaaat	ttttctgatg	tgtttattga	1020
aaaaatccaa	gtataagtgg	acttgtgcac	tcaaaccagg	gttggttcaag	ggtcaactgt	1080
gtaccacagag	ggaaacagtg	acacagattc	atagaggtga	aacacgaaga	gaaacaggaa	1140
aatcaagac	tctacaaaga	ggctgggcag	ggtggctcat	gcctgtaate	ccagcacttt	1200
gggagggcag	gcaggcagat	cacttgaggt	aaggagttca	agaccagcct	ggccaaaatg	1260
gtgaaatcct	gtctgtacta	aaaatacaaa	agtagctgg	atatggtggc	aggcgcctgt	1320
aatcccagct	acttgggagg	ctgaggcagg	agaattgctt	gaatatggga	ggcagaggtt	1380
gaagtgcgtt	gagatcacac	cactatactc	cagctggggc	aacagagtaa	gactctgtct	1440
caaaaaaaaa	aaaaaaaaa					1459

&lt;210&gt; 175

&lt;211&gt; 1167

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(1167)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 175

gcgcagccct	ggcaggcggc	actggtcatg	gaaaacgaat	tggtctgctc	gggcgtcctg	60
gtgcatccgc	agtgggtgct	gtcagccgca	cactgtttcc	agaactccta	caccatcggg	120
ctgggcctgc	acagtcttga	ggccgaccaa	gagccaggga	gccagatggg	ggaggccagc	180
ctctccgtac	ggcacccaga	gtacaacaga	ctcttgctcg	ctaaccgact	catgctcatc	240
aagttggacg	aatccgtgtc	cgagtctgac	accatccgga	gcatcagcat	tgcttcgcag	300
tgccctaccg	cggggaactc	ttgcctcgtn	tctggctggg	gtctgctggc	gaacggcaga	360
atgcctaccg	tgctgcactg	cgtgaacgtg	tcggtggtgt	ctgaggangt	ctgcagtaag	420
ctctatgacc	cgctgtacca	ccccagcatg	ttctgcgccg	gcggagggca	agaccagaag	480
gactcctgca	acggtgactc	tgggggggccc	ctgatctgca	acgggtactt	gcagggcctt	540
gtgtctttcg	gaaaagcccc	gtgtggccaa	cttgccgtgc	caggtgtcta	caccaacctc	600
tgcaaattca	ctgagtggat	agagaaaacc	gtccagncca	gttaactctg	gggactggga	660
acccatgaaa	ttgaccccca	aatacatcct	gcggaangaa	ttcaggaata	totgttccca	720
gcccctcctc	cctcaggccc	aggagtccag	gccccagccc	cctcctccct	caaaccaagg	780

```

gtacagatcc ccagcccctc ctccctcaga cccaggagtc cagaccccc agcccctcnt      840
ccntcagacc caggagtcca gccctcctc cntcagacgc aggagtccag acccccagc      900
ccntcntccg tcagaccag ggggtgcaggc ccccaacccc tcntcntca gagtccagagg      960
tccaagcccc caaccctcgt ttcccagac ccagaggtnc aggtcccagc ccctcctccc     1020
tcagaccag cgggtccaatg ccacctagan tntccctgta cacagtgcc ccttggtggca     1080
ngttgacca accttaccag ttgggttttc attttttgc cctttcccct agatccagaa     1140
ataaagtnta agagaagcgc aaaaaaa      1167

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<210> 176  
 <211> 205  
 <212> PRT  
 <213> Homo sapien

<220>  
 <221> VARIANT  
 <222> (1)...(205)  
 <223> Xaa = Any Amino Acid

```

<400> 176
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
 1          5          10          15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
 20          25          30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
 35          40          45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu
 50          55          60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
 65          70          75          80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
 85          90          95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
100          105          110
Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val
115          120          125
Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala
130          135          140
Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly
145          150          155          160
Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys
165          170          175
Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys
180          185          190
Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser
195          200          205

```

<210> 177  
 <211> 1119  
 <212> DNA  
 <213> Homo sapien

```

<400> 177
gcgcactcgc agccctggca ggcggcactg gtcattgaaa acgaattgtt ctgctcgggc      60
gtcctggtgc atccgcagtg ggtgctgtca gccgcacact gtttccagaa ctctacacc     120
atcgggctgg gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag     180
gccagcctct ccgtacggca cccagagtac aacagaccct tgctcgctaa cgacctcatg     240
ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattgct     300
tcgcagtgcc ctaccgcggg gaactcttgc ctggtttctg gctggggtct gctggcgaac     360

```

gatgctgtga	ttgccatcca	gtcccagact	gtgggaggct	gggagtgtga	gaagctttcc	420
caaccctggc	agggttgtac	catttcggca	acttccagtg	caaggacgtc	ctgctgcac	480
ctcactgggt	gtcactact	gtcactgca	tcacccggaa	cactgtgatc	aactagccag	540
caccatagtt	ctccgaagtc	agactatcat	gattactgtg	ttgactgtgc	tgtctattgt	600
actaaccatg	ccgatgttta	ggtgaaatta	gcgtcacttg	gcctcaacca	tcttggtatc	660
cagttatcct	cactgaattg	agatttcctg	cttcagtgtc	agccattccc	acataatttc	720
tgacctacag	aggtgaggga	tcatatagct	cttcaaggat	gctggtaactc	ccctcacaaa	780
ttcatttctc	ctgttgtagt	gaaagggtgcg	ccctctggag	cctcccaggg	tgggtgtgca	840
ggtcacaatg	atgaatgtat	gatcgtgttc	ccattaccca	aagcctttaa	atccctcatg	900
ctcagtacac	cagggcaggt	ctagcatttc	ttcatttagt	gtatgctgtc	cattcatgca	960
accacctcag	gactcctgga	ttctctgcct	agttgagctc	ctgcatgctg	cctccttggg	1020
gaggtgaggg	agagggccca	tggttcaatg	ggatctgtgc	agttgtaaca	cattaggtgc	1080
ttaataaaca	gaagctgtga	tgttaaaaaa	aaaaaaaa			1119

&lt;210&gt; 178

&lt;211&gt; 164

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(164)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 178

Met	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp
1				5					10					15	
Val	Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu
			20					25					30		
Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met	Val
		35					40					45			
Glu	Ala	Ser	Leu	Ser	Val	Arg	His	Pro	Glu	Tyr	Asn	Arg	Pro	Leu	Leu
	50					55					60				
Ala	Asn	Asp	Leu	Met	Leu	Ile	Lys	Leu	Asp	Glu	Ser	Val	Ser	Glu	Ser
65					70				75					80	
Asp	Thr	Ile	Arg	Ser	Ile	Ser	Ile	Ala	Ser	Gln	Cys	Pro	Thr	Ala	Gly
			85						90					95	
Asn	Ser	Cys	Leu	Val	Ser	Gly	Trp	Gly	Leu	Leu	Ala	Asn	Asp	Ala	Val
			100					105					110		
Ile	Ala	Ile	Gln	Ser	Xaa	Thr	Val	Gly	Gly	Trp	Glu	Cys	Glu	Lys	Leu
		115					120					125			
Ser	Gln	Pro	Trp	Gln	Gly	Cys	Thr	Ile	Ser	Ala	Thr	Ser	Ser	Ala	Arg
	130					135					140				
Thr	Ser	Cys	Cys	Ile	Leu	Thr	Gly	Cys	Ser	Leu	Leu	Leu	Thr	Ala	Ser
145					150					155					160
Pro	Gly	Thr	Leu												

&lt;210&gt; 179

&lt;211&gt; 250

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 179

ctggagtgcc	ttggtgtttc	aagcccttgc	aggaagcaga	atgcaccttc	tgaggcacct	60
ccagctgccc	ccggccgggg	gatgogaggc	tcggagcacc	cttgcccggc	tgtgattgct	120
gccaggcact	gttcatctca	gottttctgt	ccctttgtctc	ccggcaagcg	cttctgtctga	180
aagttcatat	ctggagcctg	atgtcttaac	gaataaaggt	cccattgctcc	acccgaaaaa	240

aaaaaaaaaa

250

<210> 180  
 <211> 202  
 <212> DNA  
 <213> Homo sapien

&lt;400&gt; 180

actagtcacag	tgtgggtggaa	ttccattgtg	ttgggcccac	cacaatggct	acctttaaca	60
tcacccagac	cccgcccctg	cccgtgcccc	acgtgctgc	taacgacagt	atgatgctta	120
ctctgctact	cggaactat	ttttatgtaa	ttaatgtatg	ctttcttgtt	tataaatgcc	180
tgatttaaaa	aaaaaaaaaa	aa				202

<210> 181  
 <211> 558  
 <212> DNA  
 <213> Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(558)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 181

tccytttgkt	naggtttkkg	agacamccck	agacctwaan	ctgtgtcaca	gacttcynng	60
aatgtttagg	cagtgttagt	aatttcytcg	taatgattct	gttattactt	tcctnattct	120
ttattcctct	ttcttctgaa	gattaatgaa	gttgaaaatt	gaggtggata	aatacaaaaa	180
ggtagtgtga	tagtataagt	atctaagtgc	agatgaaagt	gtgttatata	tatccattca	240
aaattatgca	agttagtaat	tactcaggg	taactaaatt	actttaatat	gctgttgaac	300
ctactctgtt	ccttggttag	aaaaaattat	aaacaggact	ttgttagttt	gggaagccaa	360
attgataata	ttctatgttc	taaaagttgg	gctatacata	aattattaag	aaatatggaw	420
ttttattccc	aggaatatgg	kgttcatttt	atgaatatta	cscrggatag	awgtwtgagt	480
aaaaycagtt	ttggtwaata	ygtwaatatg	tcmtaaataa	acaakgcttt	gacttatttc	540
caaaaaaaaa	aaaaaaaa					558

<210> 182  
 <211> 479  
 <212> DNA  
 <213> Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(479)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 182

acagggwttk	grggatgcta	agscocccrga	rwtygtttga	tccaaccctg	gcttwttttc	60
agaggggaaa	atggggccta	gaagttacag	mecatytagy	tggtgcgmtg	gcacccctgg	120
cstcacacag	astcccagag	agctgggact	acaggcacac	agtcactgaa	gcaggccctg	180
ttwgcaattc	acgttgccac	ctccaaactta	aacattcttc	atatgtgatg	tccttagtca	240
ctaaggttaa	actttccac	ccagaaaagg	caacttagat	aaaatcttag	agtactttca	300
tactmttcta	agtcctcttc	cagcctcact	kkgagtcctm	cytggggggt	gataggaant	360
ntctcttggc	tttctcaata	aartctctat	ycatctcatg	tttaatttgg	tacgcataara	420
awtgstgara	aaattaaaat	gttctgggtty	mactttaaaa	araaaaaaaa	aaaaaaaaaa	479

<210> 183  
 <211> 384  
 <212> DNA

<213> Homo sapien

<400> 183

aggcgggagc	agaagctaaa	gccaaagccc	aagaagagt	gcagtgccag	cactgggtgcc	60
agtaccagta	ccaataacag	tgccagtgcc	agtgccagca	ccagtgggtg	cttcagtgtc	120
ggtgccagcc	tgaccgccac	tctcacattt	gggtctctcg	ctggccttgg	tggagctggg	180
gccagcacca	gtggcagctc	tgggtgcctgt	ggtttctcct	acaagtgaga	ttttagatat	240
tgtaatacct	gccagtcttt	ctcttcaagc	caggggtgcat	cctcagaaac	ctactcaaca	300
cagcactcta	ggcagccact	atcaatcaat	tgaagttgac	actctgcatt	aratctattt	360
gccatttcaa	aaaaaaaaaa	aaaa				384

<210> 184

<211> 496

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(496)

<223> n = A,T,C or G

<400> 184

accgaattgg	gaccgctggc	ttataagcga	tcattgtynt	cgrgtatkac	ctcaacgagc	60
aggagatc	agtctatacg	ctgaagaaat	ttgaccgat	gggacaacag	acctgctcag	120
cccatcctgc	tcggttctcc	ccagatgaca	aatactctsg	acaccgaatc	accatcaaga	180
aacgcttcaa	ggtgctcatg	accagcaac	cgcgcctgt	cctctgagg	tcccttaa	240
tgatgtcttt	tctgccacct	gttaccctc	ggagactccg	taaccaaact	cttcggactg	300
tgagccctga	tgcctttttg	ccagccatac	tctttggcat	ccagtctctc	gtggcgattg	360
attatgcttg	tgtgaggcaa	tcattggtgg	atcacccata	aagggaacac	atttgacttt	420
tttttctcat	attttaaatt	actacmagaw	tattwmagaw	waaatgawtt	gaaaaactst	480
taaaaaaaaa	aaaaaa					496

<210> 185

<211> 384

<212> DNA

<213> Homo sapien

<400> 185

gctggtagcc	tatggcgkgg	cccacggagg	ggctcctgag	gccacggrac	agtgacttcc	60
caagtatcyt	gcgscgctc	ttctaccgtc	cctacctgca	gatcttcggg	cagattcccc	120
aggaggacat	ggacgtggcc	ctcatggagc	acagcaactg	ytogtcggag	cccggcttct	180
gggcacaccc	tcttggggcc	caggcgggca	cctgcgtctc	ccagtatgcc	aactggctgg	240
tgggtgctgt	cctcgtcatc	ttcctgctcg	tggccaacat	cctgctgggtc	aacttgctca	300
ttgccatgtt	cagttacaca	ttcggcaaat	tacagggcaa	cagcgatctc	tactgggaag	360
gcgcagcgtt	accgcctcat	ccgg				384

<210> 186

<211> 577

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(577)

<223> n = A,T,C or G

<400> 186

gagttagctc	ctccacaacc	ttgatgaggt	cgtctgcagt	ggcctctcgc	ttcataccgc	60
------------	------------	------------	------------	------------	------------	----



tnccatcgtc	atactgtagg	tttgccacca	cytcctggca	tcttggggcg	gcntaatatt	120
ccaggaaact	ctcaatcaag	tcaccgtcga	tgaaacctgt	gggctgggtc	tgtcttccgc	180
tcggtgtgaa	aggatctccc	agaaggagt	ctcgatcttc	cccacacttt	tgatgacttt	240
attgagtcga	ttctgcatgt	ccagcaggag	gttgtaggag	ctctctgaca	gtgagggtcac	300
cagccctatc	atgccgttga	mcgtgccgaa	garcaccgag	ccttgtgtgg	gggkkgaa	360
ctcaccaga	ttctgcatta	ccagagagcc	gtggcaaaag	acattgacaa	actcgcccag	420
gtggaaaaag	amcamctcct	ggargtgctn	gcccgtcctc	gtcmgttggt	ggcagcgctw	480
tccttttgac	acacaaacaa	gttaaaggca	ttttcagccc	ccagaaantt	gtcatcatcc	540
aagatntcgc	acagcactna	tccagttggg	attaat			577

<210> 187  
 <211> 534  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(534)  
 <223> n = A,T,C or G

<400> 187						
aacatcttcc	tgtataatgc	tgtgtaatat	cgatccgatn	ttgtctgstg	agaatycatw	60
actkggaaaa	gmaacattaa	agcctggaca	ctggtattaa	aattcacaat	atgcaacact	120
ttaaacagt	tgtcaatctg	ctcccyynac	tttgtcatca	ccagtctggg	aakaagggtg	180
tgccctattc	acacctgtta	aaaggggcgt	aagcattttt	gattcaacat	cttttttttt	240
gacacaagtc	cgaaaaaagc	aaaagtaaac	agttatyaat	ttgttagcca	attcactttc	300
ttcatgggac	agagccatyt	gatttaaaaa	gcaaattgca	taatattgag	cttygggagc	360
tgatatttga	gcggaagagt	agcctttcta	cttcaccaga	cacaactccc	tttcatattg	420
ggatgttnac	naaagtwaat	tctctwacag	atgggatgct	tttgtggcaa	ttctgttctg	480
aggatctccc	agtttattta	ccacttgcac	aagaaggcgt	tttcttcttc	agge	534

<210> 188  
 <211> 761  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(761)  
 <223> n = A,T,C or G

<400> 188						
agaaaccagt	atctctnaaa	acaacctctc	ataccttgtg	gacctaat	ttgtgtgcgtg	60
tgtgtgtg	cgcatattat	atagacaggc	acatcttttt	tactttttgta	aaagcttatg	120
cctcttttgg	atctatatct	gtgaaagttt	taatgatctg	ccataatgtc	ttggggacct	180
ttgtcttctg	tgtaaatggt	actagagaaa	acacctatnt	tatgagtcaa	tctagttngt	240
tttattcgac	atgaaggaaa	tttccagatn	acaacactna	caaactctcc	ctkgackarg	300
ggggacaaa	aaaagcaaaa	ctgamcataa	raaacaatwa	cctgggtgaga	arttgcataa	360
acagaaatwr	ggtagtatat	tgaarnacag	catcattaaa	rmgttwtktt	wttctccctt	420
gcaaaaaaca	tgtacngact	tcccgttgag	taatgccaag	ttgttttttt	tatnataaaa	480
cttgcccttc	attacatggt	tnaaagtgg	gtgggtggcc	aaaatattga	aatgatggaa	540
ctgactgata	aagctgtaca	aataagcagt	gtgcctaaca	agcaacacag	taatgttgac	600
atgcttaatt	cacaaatgct	aatttcatta	taaatgtttg	ctaaaataca	ctttgaacta	660
ttttctgt	ttcccagagc	tgagatntta	gattttatgt	agtatnaagt	gaaaaantac	720
gaaaataata	acattgaaga	aaaananaaa	aaanaaaaaa	a		761

<210> 189  
 <211> 482

<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(482)  
<223> n = A,T,C or G

<400> 189  
 tttttttttt tttgccgatn ctactatattt attgcaggan gtgggggtgt atgcaccgca 60  
 caccggggct atnagaagca agaaggaagg agggagggca cagccccttg ctgagcaaca 120  
 aagccgcctg ctgccttctc tgtctgtctc ctgggtgcagg cacatgggga gaccttcccc 180  
 aaggcagggg ccaccagtcc aggggtggga atacagggg tgggangtgt gcataagaag 240  
 tgataggcac aggccaccg gtacagaccc ctcggtcct gacaggtnga tttcgaccag 300  
 gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc 360  
 aaatttggtc ngtcatngaa ngggcanttt tccaantng gctnggtctt ggtacncttg 420  
 gttcggccca gctccncgtc caaaaantat tcaccnct ccnaattgt tgcnggnccc 480  
 cc 482

<210> 190  
<211> 471  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(471)  
<223> n = A,T,C or G

<400> 190  
 tttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtggttttg 60  
 aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtnctcca 120  
 aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag 180  
 cgcttttgac atacaatgca caaaaaaaaa aggggggggg gaccacatgg attaaaattt 240  
 taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt 300  
 tgaaaaattt catgtatgca atccaacca agaactnat tggtagatcat gantnctta 360  
 ctacatcnac cttgatcatt gccaggaacn aaaagttnaa ancacncngt acaaaaanaa 420  
 tctgtaattn anttcaacct ccgtacngaa aaatnttntt tatacactcc c 471

<210> 191  
<211> 402  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(402)  
<223> n = A,T,C or G

<400> 191  
 gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct 60  
 gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa 120  
 attcttcacc agtcacatct totaggacct ttttggtatc agttagtata agctcttcca 180  
 cttcctttgt taagacttca tctggtaaa gcttaagttt tgtagaaagg aattyaattg 240  
 ctggttctct aacaatgtcc tctccttgaa gtatttggt gaacaacca cctaaagtcc 300  
 ctttgtgcac ccatttttaa tatacttaat agggcattgk tncactaggt taaattctgc 360  
 aagagtcac tgtctgcaaa agttgcgtta gtatatctgc ca 402

<210> 192  
 <211> 601  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(601)  
 <223> n = A,T,C or G

<400> 192  
 gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact 60  
 ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac 120  
 atgcytyttt gaytaccgtg tgccaagtgc tgggtgattct yaacacacyt ccatcccgt 180  
 cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc 240  
 acgagacact tgaaagggtg aacaaagcga ytcttgcat gctttttgtc cctccggcac 300  
 cagttgtcaa tactaaccgg ctggtttgcc tccatcacat ttgtgatctg tagctctgga 360  
 tacatctcct gacagtactg aagaacttct tcttttgttt caaaagcarg tcttggtgcc 420  
 tgttggatca ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac 480  
 aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag 540  
 cctcgatgta gccggccagc gccaaaggcag gcgcctgag cccaccagc agcagaagca 600  
 g 601

<210> 193  
 <211> 608  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(608)  
 <223> n = A,T,C or G

<400> 193  
 atacagccca natcccacca cgaagatgcg cttgttgact gagaacctga tgcggtcact 60  
 ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt 120  
 cccaacgcag gcagmagcgg gcccggtcaa tgaactccay tctgtggttg gggtkgacgg 180  
 tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccagc tgtgcgggac 240  
 ctgcagcgaa actcctcgat ggtcatgagc gggaagcgaa tgaggcccag gcccttgccc 300  
 agaaccttcc gcctgttctc tggcgtcacc tgcagctgct gccgctgaca ctgggcctcg 360  
 gaccagcgga caaacggcrt tgaacagccg cacctcacgg atgcccagtg tgtcgcgctc 420  
 caggammgsc accagcgtgt ccagggtcaat gtcggtgaag ccctccgagg gtrattggcgt 480  
 ctgcagtggt tttgtcgatg ttctccaggc acaggctggc cagctgagggt tcatcgaaga 540  
 gtcgcgcctg cgtgagcagc atgaaggcgt tgtcggtcgc cagttcttct tcagggaactc 600  
 cagcgaat 608

<210> 194  
 <211> 392  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(392)  
 <223> n = A,T,C or G

<400> 194  
 gaacggctgg accttgccctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt 60

ccagtccgag	cagccccaga	ccgctgccgc	ccgaagctaa	gcctgcctct	ggccttcccc	120
tccgcctcaa	tgcagaacca	gtagtgggag	cactgtgttt	agagttaaga	gtgaacactg	180
tttgatttta	cttggaatt	tcctctgtta	tatagctttt	cccaatgcta	atttccaaac	240
aacaacaaca	aaataacatg	tttgcctgtt	aagttgtata	aaagtaggtg	attctgtatt	300
taaagaaaat	attactgtta	catatactgc	ttgcaatttc	tgtattttatt	gktnctstgg	360
aaataaatat	agttattaaa	ggttgtcant	cc			392

<210> 195  
 <211> 502  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(502)  
 <223> n = A,T,C or G

<400> 195						
ccsttkgagg	ggtkaggkyc	cagttyccga	gtggaagaaa	caggccagga	gaagtgcgtg	60
ccgagctgag	gcagatgttc	ccacagtgc	ccccagagcc	stgggstata	gtytctgacc	120
cctcncaagg	aaagaccacs	ttctggggac	atgggctgga	gggcaggacc	tagaggcacc	180
aagggaaggc	cccattccgg	ggstgttccc	cgaggaggaa	gggaaggggc	tctgtgtgcc	240
ccccasgagg	aagaggccct	gagtcctggg	atcagacacc	ccttcacgtg	tatccccaca	300
caaatgcaag	ctcaccaagg	tcccctctca	gtccccttcc	stacaccctg	amcgggccact	360
gscscacacc	caccagagc	acgccaccgc	ccatggggar	tgtgctcaag	gartcgcnng	420
gcarcgtgga	catctngtcc	cagaaggggg	cagaatctcc	aatagangga	ctgarcmstt	480
gctnanaaaa	aaaaanaaaa	aa				502

<210> 196  
 <211> 665  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(665)  
 <223> n = A,T,C or G

<400> 196						
ggttacttgg	tttcattgcc	accacttagt	ggatgtcatt	tagaaccatt	ttgtctgctc	60
cctctggaag	ccttgccgag	agcggacttt	gtaattgttg	gagaataact	gctgaatttt	120
wagctgtttk	gagttgatts	gcaccactgc	accacaact	tcaatatgaa	aacyawttga	180
actwatttat	tatcttgtga	aaagtataac	aatgaaaatt	ttgttcatac	tgtattkatc	240
aagtatgatg	aaaagcaawa	gatataatatt	cttttattat	gttaaattat	gattgccatt	300
attaatcggc	aaaatgtgga	gtgtatgttc	ttttcacagt	aatatatgcc	ttttgtaact	360
tcaacttggtt	attttattgt	aaatgartta	caaaattcct	aatttaagar	aatggtagt	420
watatttatt	tcattaat	ctttcctkgt	ttacgtwaat	tttgaaaaga	wtgcatgatt	480
tcttgacaga	aatcgatcct	gatgctgtgg	aagtagtttg	accacatcc	ctatgagttt	540
ttcttagaat	gtataaagg	tgtagcccat	cnaacttcaa	agaaaaaat	gaccacatac	600
tttgcaatca	ggctgaaatg	tggcatgctn	ttctaattcc	aactttataa	actagcaaan	660
aagtg						665

<210> 197  
 <211> 492  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature  
 <222> (1)...(492)  
 <223> n = A,T,C or G

<400> 197

tttntttttt	ttttttttgc	aggaaggatt	ccattttattg	tggatgcatt	ttcacaatat	60
atgtttattg	gagcgatcca	ttatcagtga	aaagtatcaa	gtgtttataa	natttttagg	120
aaggcagatt	cacagaacat	gctngtcngc	ttgcagtttt	acctcgtana	gatnacagag	180
aatttatagtc	naaccagtaa	acnaggaatt	tactttttcaa	aagattaaat	ccaaactgaa	240
caaaattcta	ccctgaaact	tactccatcc	aaatattgga	ataanagtca	gcagtgtatc	300
attctcttct	gaacttttaga	ttttctagaa	aaatatgtaa	tagtgatcag	gaagagctct	360
tgttcaaaag	tacaacnaag	caatgttccc	ttaccatagg	ccttaattca	aactttgatc	420
catttcactc	ccatcacggg	agtcaatgct	acctgggaca	cttgtatttt	gttcatnctg	480
ancntggctt	aa					492

<210> 198  
 <211> 478  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(478)  
 <223> n = A,T,C or G

<400> 198

tttnttttgn	atttcantct	gtannaanta	ttttcattat	gtttattana	aaaatatnaa	60
tgntccacn	acaaatcatn	ttacntnagt	aagaggccan	ctacattgta	caacatacac	120
tgagtatatt	ttgaaaagga	caagttttaa	gtanacncat	attgccganc	atancacatt	180
tatacatggc	ttgattgata	tttagcacag	canaaactga	gtgagttacc	agaaanaaat	240
natatatgtc	aatcngattt	aagatacaaa	acagatccta	tggtagatan	catcntgtag	300
gagttgtggc	tttatgttta	ctgaaagtca	atgcagttcc	tgtacaaaaga	gatggccgta	360
agcattctag	tacctctact	ccatggttaa	gaatcgtaca	cttatgttta	catatgtnc	420
gggtaagaat	tgtgttaagt	naanttatgg	agaggtccan	gagaaaaatt	tgatncaa	478

<210> 199  
 <211> 482  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(482)  
 <223> n = A,T,C or G

<400> 199

agtgacttgt	cctccaacaa	aacccttga	tcaagtttgt	ggcactgaca	atcagaccta	60
tgctagtacc	tgatcatctat	tcgctactaa	atgcagactg	gaggggacca	aaaaggggca	120
tcaactccag	ctggattatt	ttggagcctg	caaactctatt	cctacttgta	cggactttga	180
agtgattcag	tttctcttac	ggatgagaga	ctggtccaag	aatatcctca	tgcagcttta	240
tgaagccnac	tctgaacacg	ctggttatct	nagatgagaa	ncagagaaat	aaagtcnaga	300
aaatttacct	ggangaaaag	aggctttngg	ctggggacca	tccattgaa	ccttctctta	360
anggacttta	agaanaaact	accacatgtn	tgtngtatcc	tggtgccngg	ccgtttantg	420
aacntngacn	ncacccttnt	ggaatanant	cttgacngcn	tcctgaactt	gctcctctgc	480
ga						482

<210> 200  
 <211> 270

<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(270)  
<223> n = A,T,C or G

<400> 200  
cggccgcaag tgcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc 60  
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc 120  
aaggctgagc tgacgccgca gaggtcgtgt cacgtcccac gaccttgacg ccgtcgggga 180  
cagccggaac agagcccggg gaangcggga ggccctcggg agcccctcgg gaagggcggc 240  
ccgagagata cgcaggtgca ggtggccgcc 270

<210> 201  
<211> 419  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(419)  
<223> n = A,T,C or G

<400> 201  
tttttttttt ttttggaaac tactgcgagc acagcaggtc agcaacaagt ttattttgca 60  
gctagcaagg taacagggtg gggcatgggt acatgttcag gtcaacttcc ttgtcgtgg 120  
ttgattgggt tgtctttatg ggggcggggt ggggtagggg aaancgaagc anaantaaca 180  
tggagtgggt gcaccctccc tgtagaacct gggtacnaaa gottggggca gttcacctgg 240  
tctgtgaccg tcatttttctt gacatcaatg ttattagaag tcaggatata ttttagagag 300  
tccactgtnt ctggaggagg attagggttt cttgccanaa tccaancaa atccacntga 360  
aaaagtggga tgatncangt acngaatacc ganggcatan ttctcatant cgggtggcca 419

<210> 202  
<211> 509  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(509)  
<223> n = A,T,C or G

<400> 202  
tttntttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60  
tggcacttaa tccattttta tttcaaaatg tctacaaant ttnaatncnc cattatacng 120  
gtnattttnc aaaatctaaa nnttattcaa atntnagcca aantccttac ncaaattnaa 180  
tacnncnaaa aatcaaaaat atacntntct ttcagcaaac ttngttacat aaattaaaaa 240  
aatatatacg gctgggtgtt tcaaagtaca attatcttaa cactgcaaac atnttttnaa 300  
ggaactaaaa taataaaaaa cactnccgca aagggttaaag ggaacaacaa attcmtttta 360  
caacancnnc nattataaaa atcatatctc aaatcttagg ggaatatata cttcacacng 420  
ggatcttaac ttttactnca ctttgtttat ttttttanaa ccattgtntt gggcccaaca 480  
caatggnaat nccnccnncn tggaactagt 509

<210> 203  
<211> 583  
<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(583)

<223> n = A,T,C or G

<400> 203

tttttttttt	ttttttttga	ccccctctt	ataaaaaaca	agttaccatt	ttattttact	60
tacacatatt	tattttataa	ttggtattag	atattcaaaa	ggcagctttt	aaaatcaaac	120
taaatggaaa	ctgccttaga	tacataattc	ttaggaatta	gcttaaaatc	tgcttaaagt	180
gaaaatcttc	tctagctctt	ttgactgtaa	atttttgact	cttgtaaaac	atccaaattc	240
atttttcttg	tctttaaaat	tatctaattc	ttccattttt	tccctattcc	aagtcaattt	300
gcttctctag	cctcatttcc	tagctcttat	ctactattag	taagtggctt	ttttcctaaa	360
agggaaaaca	ggaagagana	atggcacaca	aaacaaacat	tttatattca	tatttctacc	420
tacgttaata	aaatagcatt	ttgtgaagcc	agctcaaaag	aaggcttaga	tccttttatg	480
tccattttag	tcactaaacg	atatcnaaag	tgccagaatg	caaaagggtt	gtgaacattt	540
attcaaaagc	taataataaga	tatttcacat	actcatcttt	ctg		583

<210> 204

<211> 589

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(589)

<223> n = A,T,C or G

<400> 204

ttttttttnt	tttttttttt	tttttttctc	ttcttttttt	ttganaatga	ggatcgagtt	60
tttcaactctc	tagatagggc	atgaagaaaa	ctcatctttc	cagcttttaa	ataacaatca	120
aatctcttat	gctatatcat	attttaagtt	aaactaatga	gtcactggct	tatcttctcc	180
tgaaggaaat	ctgttcattc	ttctcattca	tatagtтата	tcaagtacta	ccttgcatat	240
tgagagggtt	ttcttctcta	tttacacata	tatttccatg	tgaatttgta	tcaaaccctt	300
attttcatgc	aaactagaaa	ataatgtntt	cttttgcata	agagaagaga	acaatatnag	360
cattacaaaa	ctgctcaaat	tgtttgtaa	gnttatccat	tataattagt	tnggcaggag	420
ctaatacaaa	tcacatttac	ngacnagcaa	taataaaact	gaagtaccag	ttaaatatcc	480
aaaataatta	aaggaacatt	tttagcctgg	gtataattag	ctaattcact	ttacaagcat	540
ttattnagaa	tgaattcaca	tgttattatt	cctnagccca	acacaatgg		589

<210> 205

<211> 545

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(545)

<223> n = A,T,C or G

<400> 205

tttttttttt	ttttttcagt	aataatcaga	acaatattta	tttttatatt	taaaattcat	60
agaaaagtgc	cttacattta	ataaaagttt	gtttctcaaa	gtgatcagag	gaattagata	120
tngtcttgaa	caccaatatt	aatttgagga	aaatacacca	aaatacatta	agtaaattat	180
ttaagatcat	agagcttgta	agtgaaga	taaaatttga	cctcagaaac	tctgagcatt	240
aaaaatccac	tattagcaaa	taaattacta	tggtcttctt	gctttaattt	tgtgatgaat	300
atgggggtgc	actggtaaac	caacacattc	tgaaggatac	attacttagt	gatagattct	360

tatgtacttt	gctanatnac	gtggatatga	gttgacaagt	ttctctttct	tcaatctttt	420
aaggggcnaga	ngaaatgagg	aagaaaagaa	aaggattacg	catactgttc	tttctatngg	480
aaggattaga	tatgtttcct	ttgccaatat	taaaaaata	ataatgttta	ctactagtga	540
aaccc						545

<210> 206  
 <211> 487  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(487)  
 <223> n = A,T,C or G

<400> 206						
tttttttttt	tttttttagtc	aagttttctna	tttttattat	aattaaagtc	ttgggtcattt	60
cattttattag	ctctgcaact	tacatattta	aattaaagaa	acgttnttag	acaactgtna	120
caatttataa	atgtaagggtg	ccattattga	gtanatata	tcctccaaga	gtggatgtgt	180
cccttctccc	accaactaat	gaancagcaa	cattagttaa	atatttattag	tagatnatac	240
actgctgcaa	acgctaattc	tcttctccat	ccccatgtng	atattgtgta	tatgtgtgag	300
ttggtnagaa	tgcatcanca	atctnacaat	caacagcaag	atgaagctag	gcntgggctt	360
tcggtgaaaa	tagactgtgt	ctgtctgaat	caaagtatct	gacctatcct	cgggtggcaag	420
aactcttcga	accgcttcct	caaaggcngc	tgccacattt	gtggcntctn	ttgcacttgt	480
ttcaaaa						545

<210> 207  
 <211> 332  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(332)  
 <223> n = A,T,C or G

<400> 207						
tgaattggct	aaaagactgc	atttttanaa	ctagcaactc	ttatttcttt	cctttaaaaa	60
tacatagcat	taaatcccaa	atcctattta	aagacctgac	agcttgagaa	ggctactact	120
gcatttatag	gcacttctgg	tggttctgct	gttacntttg	aantctgaca	atccttgana	180
atctttgcat	gcagaggagg	taaaagggtat	tggattttca	cagaggaana	acacagcgca	240
gaaatgaagg	ggccaggctt	actgagcttg	tccactggag	ggctcatggg	tgggacatgg	300
aaaagaaggc	agcctaggcc	ctggggagcc	ca			332

<210> 208  
 <211> 524  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(524)  
 <223> n = A,T,C or G

<400> 208						
agggcgtggg	gcggagggcg	ttactgtttt	gtctcagtaa	caataaatac	aaaaagactg	60
gttggtttcc	ggcccatcc	aaccacgaag	ttgatttctc	ttgtgtgcag	agtgactgat	120
tttaaaggac	atggagcttg	tcacaatgtc	acaatgtcac	agtgtgaagg	gcacactcac	180



```

tcccgctga ttcacattta gcaaccaaca atagctcatg agtccatact tgtaaatact 240
tttggcagaa tacttnttga aacttgacaga tgataactaa gatccaagat atttcccaaa 300
gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca ttacaagtc 360
atgagccag acactgacat caaactaagc ccacttagac tctcaccac cagtctgtcc 420
tgtcatcaga caggaggetg tcaccttgac caaattctca ccagtcaatc atctatccaa 480
aaaccattac ctgatccact tccggtaatg caccaccttg gtga 524

```

```

<210> 209
<211> 159
<212> DNA
<213> Homo sapien

```

```

<400> 209
gggtgaggaa atccagagtt gccatggaga aaattccagt gtcagcattc ttgtctcttg 60
tggccctctc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaggaca 120
caaaggactc tcgacccaaa ctgccccaga cctctctcca 159

```

```

<210> 210
<211> 256
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(256)
<223> n = A,T,C or G

```

```

<400> 210
actccctggc agacaaaggc agaggagaga gctctgttag ttctgtgttg ttgaactgcc 60
actgaatttc tttccacttg gactattaca tgccanttga gggactaatg gaaaaacgta 120
tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat 180
ttgcaggggtg naaatgggan ggctgggttg ttanatgaac agggacatag gaggtaggca 240
ccaggatgct aaatca 256

```

```

<210> 211
<211> 264
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(264)
<223> n = A,T,C or G

```

```

<400> 211
acattgtttt ttgagataa agcattgaga gagctctcct taacgtgaca caatggaagg 60
actggaacac ataccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt 120
atattcaagc acatattgta tatattattc agttccatgt ttatagccta gttaaggaga 180
ggggagatac attcngaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga 240
aaaaaaggag caaatgagaa gcct 264

```

```

<210> 212
<211> 328
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature

```

&lt;222&gt; (1)...(328)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 212

acccaaaaat ccaatgctga atatttggt tcattattcc canattcttt gattgtcaaa	60
ggattttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag	120
gtttatataat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccggcag	180
ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta	240
cccctacnac tctttactct ctgganaggg ccagtggtgg tagctataag cttggccaca	300
tttttttttc ctttattcct ttgtcaga	328

&lt;210&gt; 213

&lt;211&gt; 250

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(250)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 213

acttatgagc agagcgacat atccnagtgt agactgaata aaactgaatt ctctccagtt	60
taaagcattg ctactgaag ggatagaagt gactgccagg agggaaagta agccaaggct	120
cattatgcca aagganatat acattttcaat tctccaaact tcttctcat tccaagagtt	180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatata tctctnacct	240
tctcatcggt	250

&lt;210&gt; 214

&lt;211&gt; 444

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(444)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 214

accagaatc caatgctgaa tatttggett cattattccc agattctttg attgtcaaag	60
gatttaaatg tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg	120
tttatataat cagcaacaat attcaagcgc gacaacaggc tattgaactt gcccgccagt	180
tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac	240
ccctacgact ctttactctc tggagagggc cagtggtggg agctataagc ttggccacat	300
ttttttttcc ttatttcctt tgtcagagat gcgattcatc catatgctan aaaccaacag	360
agtgaacttt acaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt	420
actttgctct ccctaataata cctc	444

&lt;210&gt; 215

&lt;211&gt; 366

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(366)

&lt;223&gt; n = A,T,C or G

<400> 215  
 acttatgagc agagcgacat atccaagtgt anactgaata aaactgaatt ctctccagtt 60  
 taaagcattg ctactgaag ggatagaagt gactgccagg agggaaagta agccaaggct 120  
 cattatgcc aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt 180  
 ttcaatattt gcatgaacct gctgataagc catgttgaga aacaaatata tctctgacct 240  
 tctcatcggt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa 300  
 tccaagctgt tttctacact gtaaccaggt ttccaaccaa ggtggaaatc tcctatactt 360  
 ggtgcc 366

<210> 216  
 <211> 260  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(260)  
 <223> n = A,T,C or G

<400> 216  
 ctgtataaac agaactccac tgcangaggg agggccgggc caggagaatc tccgcttgtc 60  
 caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc atttttttat 120  
 taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa 180  
 atcaaaaatt tcctnaagtt ntcaagctat catatatact ntatcctgaa aaagcaacat 240  
 aatttcttct tccctccttt 260

<210> 217  
 <211> 262  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(262)  
 <223> n = A,T,C or G

<400> 217  
 acctacgtgg gtaagtttan aaatgttata atttcaggaa naggaacgca tataattgta 60  
 tcttgccat aattttctat tttaataagg aaatagcaaa ttgggggtggg gggaatgtag 120  
 ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt 180  
 atgaataatc tgtatgatta tatgtctcta gagtagattt ataattagcc acttacccta 240  
 atatccttca tgcttgtaaa gt 262

<210> 218  
 <211> 205  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(205)  
 <223> n = A,T,C or G

<400> 218  
 accaaggtgg tgcattaccg gaantggatc aangacacca tegtggccaa cccctgagca 60  
 cccctatcaa ctcccttttg tagtaaactt ggaaccttgg aaatgaccag gccaaagactc 120  
 aggctcccc agttctactg acctttgtcc ttangtntna ngtcagggt tgctaggaaa 180  
 anaaatcagc agacacaggt gtaaa 205

<210> 219  
<211> 114  
<212> DNA  
<213> Homo sapien

<400> 219  
tactgttttg tctcagtaac aataaatāca aaaagactgg ttgtgttccg gccccatcca 60  
accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga 114

<210> 220  
<211> 93  
<212> DNA  
<213> Homo sapien

<400> 220  
actagccagc acaaaaggca gggtagcctg aattgctttc tgctctttac atttctttta 60  
aaataagcat ttagtgctca gtccctactg agt 93

<210> 221  
<211> 167  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(167)  
<223> n = A,T,C or G

<400> 221  
actangtgca ggtgcgcaca aatatttgtc gatattccct tcatottgga ttccatgagg 60  
tcttttgccc agcctgtggc tctactgtag taagtttctg ctgatgagga gccagnatgc 120  
ccccactac cttccctgac gctcccana aatcacccaa cctctgt 167

<210> 222  
<211> 351  
<212> DNA  
<213> Homo sapien

<400> 222  
agggcgtggt gcgaggggcg gtactgacct cattagtagg aggatgcatt ctggcacccc 60  
gttcttcacc tgtcccccaa tctttaaag gccatactgc ataaagtcaa caacagataa 120  
atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa 180  
ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt 240  
taggtgagca tgattagaga gcttgtaggt tgcttttaca tatactctggc atatttgagt 300  
ctcgtatcaa aacaatagat tggtaaaggt ggtattattg tattgataag t 351

<210> 223  
<211> 383  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(383)  
<223> n = A,T,C or G

<400> 223

aaaacaaaca	aacaaaaaaa	acaattcttc	attcagaaaa	attatcttag	ggactgatat	60
tggttaattat	ggtcaattta	atwrrtrttkt	ggggcatttc	cttacattgt	cttgacaaga	120
ttaaaatgtc	tgtgccaaaa	ttttgtattt	tatttgaggaga	cttcttatca	aaagtaatgc	180
tgccaaagga	agtctaaggga	attagtagtg	ttcccmctcac	ttgtttggag	tgtgctattc	240
taaaagattt	tgatttcctg	gaatgacaat	tatatittaa	ctttgggtggg	ggaaanagtt	300
ataggaccac	agtcttctact	tctgatactt	gtaaattaat	cttttattgc	acttgttttg	360
accattaagc	tatatgttta	aaa				383

&lt;210&gt; 224

&lt;211&gt; 320

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 224

cccctgaagg	cttcttggtta	gaaaatagta	cagttacaac	caataggaac	aacaaaaaga	60
aaaagtgtgt	gacattgtag	tagggagtgt	gtaccctta	ctcccatca	aaaaaaaaat	120
ggatacatgg	ttaaaggata	raagggcaat	attttatcat	atgtttctaaa	agagaaggaa	180
gagaaaatac	tactttctcr	aaatggaagc	ccttaaaggt	gctttgatac	tgaaggacac	240
aaatgtggcc	gtccatcctc	ctttaragtt	gcattgacttg	gacacggtaa	ctgttgagc	300
tttaractcm	gcattgtgac					320

&lt;210&gt; 225

&lt;211&gt; 1214

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 225

gaggactgca	gcccgcactc	gcagccctgg	caggcggcac	tggtcatgga	aaacgaattg	60
ttctgtctcg	gcgtcctggg	gcacccgcag	tgggtgctgt	cagccgcaca	ctgtttccag	120
aactcctaca	ccatcgggct	gggcctgcac	agtcttgagg	ccgaccaaga	gccagggagc	180
cagatgggtg	aggccagcct	ctccgtacgg	caccagagat	acaacagacc	cttgctcgct	240
aacgacctca	tgctcatcaa	gttgagcgaa	tccgtgtccg	agtctgacac	catccggagc	300
atcagcattg	cttcgcagtg	ccctaccgcg	gggaactctt	gcctcgtttc	tggtggtggg	360
ctgctggcga	acggcagaat	gcctaccgtg	ctgcagtgcg	tgaacgtgtc	ggtggtgtct	420
gaggaggtct	gcagtaagct	ctatgaccgg	ctgtaccacc	ccagcatgtt	ctgcgcgggc	480
ggagggcaag	accagaagga	ctcctgcaac	ggtgactctg	ggggggccct	gatctgcaac	540
gggtacttgc	agggccttgt	gtctttcgga	aaagcccggt	gtggccaagt	tggcgtgcca	600
ggtgtctaca	ccaacctctg	caaattcact	gagtggtatg	agaaaaccgt	ccaggccagt	660
taactctggg	gactgggaac	ccatgaaatt	gacccccaaa	tacatcctgc	gggaaggatt	720
caggaatatc	tggtcccagc	ccctcctccc	tcaggcccag	gagtcagggc	ccccagcccc	780
tcctccctca	aaccaagggt	acagatcccc	agccctcctc	ccctcagacc	caggagtcca	840
gacccccag	cccctcctcc	ctcagaccca	ggagtccagc	ccctcctccc	tcagaccag	900
gagtcagac	ccccagccc	ctcctccctc	agaccagggg	gtccaggccc	ccaaccctc	960
ctccctcaga	ctcagagggt	caagccccca	acccctcctt	ccccagacc	agaggtccag	1020
gtcccagccc	ctcctccctc	agaccagcgg	gtccaatgcc	acctagactc	tcctgtaca	1080
cagtgcctcc	ttgtggcag	ttgacccaac	cttaccagtt	ggtttttcat	tttttgtccc	1140
tttcccttag	atccagaaat	aaagtctaag	agaagcgcaa	aaaaaaaaaa	aaaaaaaaaa	1200
aaaaaaaaaa	aaaa					1214

&lt;210&gt; 226

&lt;211&gt; 119

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 226

accagtatg	tgacgggaga	cggaacccca	tgtgacagcc	cactccacca	gggttcccaa	60
agaacctggc	ccagtcataa	tcattcatcc	tgacagtggc	aataatcacg	ataaccagt	119

<210> 227  
 <211> 818  
 <212> DNA  
 <213> Homo sapien

<400> 227  
 acaattcata gggacgacca atgaggacag ggaatgaacc cggtctctcc ccagccctga 60  
 tttttgctac atatggggtc ctttttcatt ctttgcaaaa acactgggtt ttctgagaac 120  
 acggacggtt cttagcaciaa tttgtgaaat ctgtgtaraa ccgggctttg caggggagat 180  
 aattttcctc ctctggagga aaggtggtga ttgacaggca gggagacagt gacaaggcta 240  
 gagaaagcca cgctcggcct tctctgaaac aggatggaac ggcagacccc tgaaaacgaa 300  
 gcttgctccc ttccaatcag ccacttctga gaacccccat ctaacttcct actggaaaag 360  
 agggcctcct caggagcagt ccaagagttt tcaaagataa cgtgacaact accatctaga 420  
 ggaaagggtg caccctcagc agagaagccg agagcttaac tctggctcgt tccagagaca 480  
 acctgctggc tgtcttgga tgcgccagc ctttgagagg ccactacccc atgaacttct 540  
 gccatccact ggacatgaag ctgaggacac tgggcttcaa cactgagttg tcatgagagg 600  
 gacaggctct gccctcaagc cggctgaggg cagcaaccac tctcctcccc tttctcacgc 660  
 aaagccattc ccacaaatcc agaccatacc atgaagcaac gagacccaaa cagtttggtc 720  
 caagaggata tgaggactgt ctgagcctgg ctttgggctg acaccatgca cacacacaag 780  
 gtccacttct aggttttcag cctagatggg agtcgtgt 818

<210> 228  
 <211> 744  
 <212> DNA  
 <213> Homo sapien

<400> 228  
 actggagaca ctggtgaact tgatcaagac ccagaccacc ccaggtctcc ttctgaggat 60  
 gtcatgacgt ttgacatacc tttggaacga gcctcctcct tggaagatgg aagacagtgt 120  
 tcgtggccga cctggcctct cctggcctgt ttcttaagat gcggagtcac atttcaatgg 180  
 taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga 240  
 tgctcgggtc acattggggt gctttgggat aaaagattta tgagccaact attctctggc 300  
 accagattct aggccagttt gttccaactga agcttttccc acagcagtcc acctctgcag 360  
 gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt 420  
 gagaaggcta ggatgcttgt ctagtgttct tagctgtcac gttggctcct tccaggttgg 480  
 ccagacgggtg ttggccactc ccttctaaaa cacaggcgcc ctccctgggtga cagtgacccg 540  
 ccgtgggtatg ccttggccca ttccagcagt ccaggttatg catttcaagt ttgggggttg 600  
 ttcttttctg taatgttctt ctgtgttgtc agctgtcttc atttcctggg ctaagcagca 660  
 ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt 720  
 cttcactctg aagtagctgg tggt 744

<210> 229  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<400> 229  
 cgagtctggg ttttgtctat aaagtttgat ccctcctttt ctcatccaaa tcatgtgaac 60  
 cattacacat cgaaataaaa gaaaggtggc agacttgccc aacgccaggc tgacatgtgc 120  
 tgcagggttg ttgtttttta attattattg ttagaaacgt caccacagc cctgttaaat 180  
 ttgtatgtga cagccaactc tgagaaggct ctatttttcc acctgcagag gatccagtct 240  
 cactaggctc ctcttgccc tcacactgga gtctccgcca gtgtgggtgc ccactgacat 300

<210> 230  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

&lt;400&gt; 230

cagcagaaca	aatacaaata	tgaagagtgc	aaagatctca	taaaatctat	gctgaggaat	60
gagcgacagt	tcaaggagga	gaagcttgca	gagcagctca	agcaagctga	ggagctcagg	120
caatataaag	tcctgggttca	cactcaggaa	cgagagctga	cccagttaag	ggagaagttg	180
cggaaggga	gagatgcctc	cctctcattg	aatgagcatc	tccaggccct	cctcactccg	240
gatgaaccgg	acaagtccca	ggggcaggac	ctccaagaaa	cagacctcgg	ccgcgaccac	300
g						301

&lt;210&gt; 231

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 231

gcaagtacgc	tggcaaactct	ctgtcaggtc	agctccagag	aagccattag	tcatttttagc	60
caggaactcc	aagtccacat	ccttggcaac	tggggacttg	cgcaggttag	ccttgaggat	120
ggcaacacgg	gacttctcat	caggaagtgg	gatgtagatg	agctgatcaa	gacggccagg	180
tctgaggatg	gcaggatcaa	tgatgtcagg	ccggttggtg	ccgccaatga	tgaacacatt	240
tttttttgtg	gacatgccat	ccatttctgt	caggatctgg	ttgatgactc	ggtcagcagc	300
c						301

&lt;210&gt; 232

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 232

agtaggtatt	tcgtgagaag	ttcaacacca	aaactggaac	atagttctcc	ttcaagtgtt	60
ggcgacagcg	gggcttcctg	attctggaat	ataactttgt	gtaaattaac	agccacctat	120
agaagagtcc	atctgctgtg	aaggagagac	agagaactct	gggttccgtc	gtcctgtcca	180
cgtgctgtac	caagtgtctg	tgccagcctg	ttacctgttc	tactgaaaa	tctggctaata	240
gctcttgtgt	atcacttctg	attctgacaa	tcaatcaatc	aatggcctag	agcactgact	300
g						301

&lt;210&gt; 233

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 233

atgactgact	tcccagtaag	gctctctaag	gggtaagtag	gaggatccac	aggattttgag	60
atgctaaggc	cccagagatc	gtttgatcca	accctcttat	tttcagaggg	gaaaatgggg	120
cctagaagtt	acagagcatc	tagctgggtc	gctggcacco	ctggcctcac	acagactccc	180
gagtagctgg	gactacaggc	acacagtcac	tgaagcaggc	cctgttagca	attctatgcg	240
tacaaattaa	catgagatga	gtagagactt	tattgagaaa	gcaagagaaa	atcctatcaa	300
c						301

&lt;210&gt; 234

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 234

aggctctaca	catcgagact	catccatgat	tgatatgaat	ttaaaaatta	caagcaaaga	60
cattttatcc	atcatgatgc	tttcttttgt	ttcttctttt	cgttttcttc	tttttctttt	120
tcaatttcag	caacatactt	ctcaatttct	tcaggattta	aaatcttgag	ggattgatct	180
cgctcatga	cagcaagttc	aatgtttttg	ccacctgact	gaaccacttc	caggagtgcc	240
ttgatcacca	gcttaatggg	cagatcatct	gcttcaatgg	cttcgtcagt	atagttcttc	300

t

301

<210> 235  
 <211> 283  
 <212> DNA  
 <213> Homo sapien

<400> 235  
 tggggctgtg catcaggcgg gtttgagaaa tattcaattc tcagcagaag ccagaatttg 60  
 aattccctca tcttttaggg aatcattttac caggtttgga gaggattcag acagctcagg 120  
 tgctttcact aatgtctctg aacttctgtc cctctttgtt catggatagt ccaataaata 180  
 atgttatctt tgaactgatg ctcataaggag agaataataag aactctgagt gatatcaaca 240  
 ttagggattc aaagaaatat tagatttaag ctcacactgg tca 283

<210> 236  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 236  
 aggtcctcca ccaactgcct gaagcacggt taaaattggg aagaagtata gtgcagcata 60  
 aatactttta aatcgatcag atttccctaa cccacatgca atcttcttca ccagaagagg 120  
 tcggagcagc atcattaata ccaagcagaa tgcgtaatag ataaatacaa tggatatatag 180  
 tgggtagacg gcttcatgag tacagtgtac tgtggtatcg taatctggac ttgggttgta 240  
 aagcatcgtg taccagtcag aaagcatcaa tactcgacat gaacgaatat aaagaacacc 300  
 a. 301

<210> 237  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 237  
 cagtggtagt ggtggtggac gtggcggttg tctgtggtgcc ttttttggtg ccogtcacaa 60  
 actcaatttt tggtcgctcc tttttggcct ttccaattt gtccatctca attttctggg 120  
 ccttggtctaa tgctcatag taggagtcct cagaccagcc atggggatca aacatatcct 180  
 ttgggtagtt ggtgccaaagc tctgcaatgg cacagaatgg atcagcttct cgtaaatacta 240  
 gggttccgaa attcttttct cctttggata atgtagttca tatccattcc ctcctttatc 300  
 t 301

<210> 238  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 238  
 gggcagggtt tttttttttt ttttttgatg gtgcagaccc ttgctttatt tgtctgactt 60  
 gttcacagtt cagccccctg ctcagaaaac caacgggcca gctaaggaga ggaggaggca 120  
 ccttgagact tccggagtcg aggtcttcca ggggtcccca gcccatcaat cattttctgc 180  
 accccctgcc tgggaagcag ctccctgggg ggtgggaatg ggtgactaga agggatttca 240  
 gtgtgggacc caggggtctgt tcttcacagt aggaggtgga agggatgact aatttcttta 300  
 t 301

<210> 239  
 <211> 239  
 <212> DNA  
 <213> Homo sapien



&lt;400&gt; 239

ataagcagct	aggggaattct	ttatttagta	atgtcctaac	ataaaagttc	acataactgc	60
ttctgtcaaa	ccatgatact	gagctttgtg	acaacccaga	aataactaag	agaaggcaaa	120
cataatacct	tagagatcaa	gaaacattta	cacagttcaa	ctgtttaaaa	atagctcaac	180
attcagccag	tgagtagagt	gtgaatgcc	gcatacacag	tatacaggtc	cttcaggga	239

&lt;210&gt; 240

&lt;211&gt; 300

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 240

ggtcctaag	aagcagcagc	ttccacattt	taacgcaggt	ttacgggtgat	actgtccttt	60
gggatctgcc	ctccagtgg	accttttaag	gaagaagtgg	gcccaagcta	agttccacat	120
gctgggtgag	ccagatgact	tctgttccct	ggtcactttc	ttcaatgggg	cgaatggggg	180
ctgccaggtt	tttaaaatca	tgcttcatct	tgaagcacac	ggtcacttca	ccctcctcac	240
gctgtgggtg	tactttgatg	aaaataccca	ctttgttggc	ctttctgaag	ctataatgtc	300

&lt;210&gt; 241

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 241

gaggtctggt	gctgaggtct	ctgggctagg	aagaggagtt	ctgtggagct	ggaagccaga	60
cctcttttga	ggaaactcca	gcagctatgt	tggtgtctct	gaggggaatgc	aacaaggctg	120
ctcctccatg	tattggaaaa	ctgcaaactg	gactcaactg	gaaggaagtg	ctgctgccag	180
tgtgaagaac	cagcctgagg	tgacagaaac	ggaagcaaac	aggaacagcc	agtcttttct	240
tcctcctcct	gtcatacggg	ctctctcaag	catcctttgt	tgtcagggggc	ctaaaaggga	300
g						301

&lt;210&gt; 242

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 242

ccgaggtcct	gggatgcaac	caatcactct	gtttcacgtg	acttttatca	ccatacaatt	60
tgtggcattt	cctcattttc	tacattgtag	aatcaagagt	gtaaataaat	gtatatcgat	120
gtcttcaaga	atatatcatt	cctttttcac	tagaaccat	tcaaaatata	agtcaagaat	180
cttaatatca	acaaatatat	caagcaaact	ggaaggcaga	ataactacca	taatttagta	240
taagtaccca	aagttttata	aatcaaaagc	cctaatagata	accattttta	gaattcaatc	300
a						301

&lt;210&gt; 243

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 243

aggtaagtcc	cagtttgaag	ctcaaaagat	ctggatagag	catagggtca	tcgacgacat	60
ggtggcccaa	gctatgaaat	cagagggagg	cttcatctgg	gcctgtaaaa	actatgatgg	120
tgacgtgcag	tcggactctg	tggcccaagg	gtatggctct	ctcggcatga	tgaccagcgt	180
gctggtttgt	ccagatggca	agacagtaga	agcagaggct	gccacggga	ctgtaaccgg	240
tcactaccgc	atgttccaga	aaggacagga	gacgtccacc	aatccattg	cttccatttt	300
t						301

&lt;210&gt; 244

<211> 300  
 <212> DNA  
 <213> Homo sapien

<400> 244  
 gctgggttgc aagaatgaaa tgaatgattc tacagctagg acttaacott gaaatggaaa 60  
 gtcatgcaat cccatttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc 120  
 ccaggacct tggaaacagt tgacactgta aggtgcttgc tccccaagac acatcctaaa 180  
 aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc ctttcttatt tatgtgaaca 240  
 actgtttgtc ttttgtgtat cttttttaa ctgtaaagtt caattgtgaa aatgaatatc 300

<210> 245  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 245  
 gtctgagtat ttaaaatggt attgaaatta tccccaacca atgtagaaa agaaagaggt 60  
 tatatactta gataaaaaat gaggtgaatt actatccatt gaaatcatgc tcttagaatt 120  
 aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat 180  
 gttttcaaag agcagagatg caattaaata ttgttttagca tcaaaaaggc cactcaatc 240  
 agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa 300  
 g 301

<210> 246  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 246  
 ggtctgtcct acaatgcctg cttcttgaaa gaagtoggca ctttctagaa tagctaaata 60  
 acctgggctt attttaaaga actatttgta gctcagattg gttttcctat ggctaaaata 120  
 agtgcttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac 180  
 taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc 240  
 caaatgtgtc ttacaaaaca cgttcctaac aaggtatgct ttacactacc aatgcagaaa 300  
 c 301

<210> 247  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 247  
 aggtcctttg gcagggtcga tggatcagag ctcaaactgg agggaaaggc atttcgggta 60  
 gcctaagagg gcgactggcg gcagcacaac caaggaaggc aaggttggtt cccccacgct 120  
 gtgtcctgtg ttcagggtcg acacacaatc ctcatgggaa caggatcacc catgcgctgc 180  
 ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg ggttccttgc 240  
 cttttcaaac catgaagtca ggctctgtat ccctcctttt cctaactgat attctaacta 300  
 a 301

<210> 248  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 248  
 aggtccttgg agatgccatt tcagccgaag gactcttctw ttcggaagta caccctcact 60  
 attaggaaga ttcttagggg taatttttct gaggaaggag aactagccaa cttaagaatt 120

acaggaagaa agtgggttgg aagacagcca aagaaataaa agcagattaa attgtatcag 180  
 gtacattcca gcctgttggc aactccataa aaacatttca gatttttaatc ccgaatttag 240  
 ctaatgagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc 300  
 c 301

<210> 249  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 249  
 gtccagagga agcacctggg gctgaactag gcttgccctg ctgtgaactt gcacttggag 60  
 ccctgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgccccgcc 120  
 ccaggagagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc 180  
 catcgtaatg aattattttg aaaattaatt ccaaccatcct ttcagattct ggatggaaag 240  
 actgaatcct tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt 300  
 a 301

<210> 250  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 250  
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 cttatcttta ttggcttgat aaacataatt atttctaaca ctagcttatt tccagttgcc 120  
 cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac 180  
 ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta 240  
 caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc 300  
 a 301

<210> 251  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 251  
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 agacaacctc atagagcata ggagaactgg ttgccctggg ggcaggggga ctgtctggat 120  
 ggcaggggtc ctcaaaaatg ccaactgtcac tgccaggaaa tgcttctgag cagtacacct 180  
 cattgggata aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccgaa 240  
 cctctggagg ggggcagtgg aatcccagct ccaggacgga tctgtctgaa aagatatcct 300  
 c 301

<210> 252  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 252  
 gcaaccaatc actctgtttc acgtgacttt tatcaccata caatttgtgg catttctca 60  
 tttttacat tgtagaatca agagtgtaaa taaatgtata tcgatgtctt caagaatata 120  
 tcatttcctt ttcactagga acccattcaa aatataagtc aagaatotta atatcaacaa 180  
 atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag tacccaaagt 240  
 tttataaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaatc 300  
 a 301

<210> 253

<211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 253  
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 caactaaaaa aaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctcccttagct 120  
 tggctctgatt gttttcagac cttaaaatat aaacttggtt cacaagcttt aatccatgtg 180  
 gatttttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt 240  
 tccatagtgc ccacagggtg ttctcacat tttctccata ggaaaatgct ttttccaag 300  
 g 301

<210> 254  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 254  
 cgctgcgcct ttcccttggg ggaggggcaa ggccagaggg ggtccaagtg cagcacgagg 60  
 aacttgacca attcccttga agcgggtggg ttaaaccctg taaatgggaa caaaatcccc 120  
 ccaaattctct tcatcttacc ctggtggact cctgactgta gaattttttg gttgaaacaa 180  
 gaaaaaataa agcttttggg cttttcaagg ttgcttaaca ggtactgaaa gactggcctc 240  
 acttaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc 300  
 t 301

<210> 255  
 <211> 302  
 <212> DNA  
 <213> Homo sapien

<400> 255  
 agcttttttt tttttttttt tttttttttt ttcattaaaa aatagtgtct tttattataa 60  
 attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagtt tgacttggtat 120  
 tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtagggggg 180  
 aggaaaaagg actggaggtg gaatctttat aaaaaacaag agtgattgag gcagattgta 240  
 aacattatta aaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac 300  
 aa 302

<210> 256  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A, T, C or G

<400> 256  
 gttccagaaa acattgaagg tggtttccca aagtctaact agggataccc cctctagcct 60  
 aggaccctcc tccccacacc tcaatccacc aaaccatcca taatgcaccc agataggccc 120  
 acccccacaaa gcctggacac cttgagcaca cagttatgac caggacagac tcatctctat 180  
 aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt 240  
 gtggcctctc ggcttggtta gcaagaacat tcagggttag cctaagttan tcgtgttagt 300  
 t 301

<210> 257  
 <211> 301

<212> DNA  
<213> Homo sapien

<400> 257

gttggtggagg aactctggct tgctcattaa gtctactga ttttcactat cccctgaatt	60
tccccactta tttttgtctt tcaactatcg aggccctaga agaggtctac ctgcctccag	120
tcttacctag tccagtctac cccctggagt tagaatggcc atcctgaagt gaaaagtaat	180
gtcacattac tcccttcagt gattttcttg agaagtgcc atccctgaat gccaccaaga	240
tcttaatctt cacatcttta atcttatctc tttagactcct ctttacaccg gagaaggctc	300
c	301

<210> 258  
<211> 301  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 258

cagcagtagt agatgccgta tgccagcacg cccagcactc ccaggatcag caccagcacc	60
aggggcccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc	120
cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaagat cttaacactg	180
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat	240
cggtgatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac	300
t	301

<210> 259  
<211> 301  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 259

tcatatatgc aaacaaatgc agactangcc tcaggcagag actaaaggac atctcttggg	60
gtgtcctgaa gtgatttgga cccctgaggg cagacaccta agtaggaatc ccagtgggaa	120
gcaaagccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggctctgt	180
tccagctcac atctcatctg catgcagcac ggaccggatg cgcccactgg gtcttggtt	240
ccctcccatc ttctcaagca gtgtccttgt tgagccattt gcattccttg ctccagggtg	300
c	301

<210> 260  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 260

ttttttttct ccctaaggaa aaagaaggaa caagtctcat aaaaccaa at aagcaatggt	60
aagggtgtctt aacttgaaaa agattaggag tcaactggtt acaagttata attgaatgaa	120
agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaaca caggattaac	180
tagggcaaaa taaataagtg tgtggaagcc ctgataagt cttaataaac agactgattc	240
actgagacat cagtacctgc ccgggcggcc gctcgagccg aattctgcag atatccatca	300

c

301

<210> 261  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 261  
 aaatatttoga gcaaatcctg taactaatgt gtctccataa aaggctttga actcagtga 60  
 tctgcttcca tccacgattc tagcaatgac ctctcggaca tcaaagctcc tcttaagggt 120  
 agcaccaact attccatata attcatcagc aggaaataaa ggctcttcag aagggttcaat 180  
 ggtgacatcc aattttcttct gataatttag attcctcaca accttcctag ttaagtgaag 240  
 ggcatgatga tcatccaaag ccagtggtc acttactcca gactttctgc aatgaagatc 300  
 a 301

<210> 262  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 262  
 gaggagagcc tggtacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc 60  
 tgtgagcttc ttgccgcaag tctctcagaa atttaaaaag atgcaaatacc ctgagtcacc 120  
 cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcaactctgca tttgtaatga 180  
 gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgcc 240  
 catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat 300  
 c 301

<210> 263  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 263  
 tttagcttgt ggtaaattgac tcacaaaact gattttaaaa tcaagttaat gtgaattttg 60  
 aaaattacta cttaatccta attcacaata acaatggcat taaggtttga cttgagttgg 120  
 ttcttagtat tatttatggg aaataggctc ttaccacttg caaataactg gccacatcat 180  
 taatgactga cttccagta aggtctctca aggggtaagt angaggatcc acaggatttg 240  
 agatgctaag gcccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg 300  
 g 301

<210> 264  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 264  
 aaagacgtta aaccactcta ctaccacttg tggaactctc aaagggtaaa tgacaaascc 60  
 aatgaatgac tctaaaaaca atattttacat ttaatggttt gtagacaata aaaaaacaag 120  
 gtggatagat ctagaattgt aacattttta gaaaaccata scatttgaca gatgagaaag 180  
 ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac 240  
 acccttcata taaattcact atcttggctt gaggcactcc ataaaatgta tcacgtgcat 300  
 a 301

<210> 265  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 265  
 tgcccaagtt atgtgtaagt gtatccgcac ccagaggtaa aactacactg tcatctttgt 60  
 cttcttgtga cgcagtatct cttctctggg gagaagccgg gaagtcttct cctggctcta 120  
 catattcttg gaagtctcta atcaactttt gttccatttg tttcatttct tcaggaggga 180  
 ttttcagttt gtcaacatgt tctctaaca cacttgcca tttctgtaaa gaatccaaag 240  
 cagtccaagg ctttgacatg tcaacaacca gcataactag agtatccttc agagatacgg 300  
 c 301

<210> 266  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 266  
 taccgtctgc ctttctccc atccaggcca tctgcgaatc tacatgggtc ctcctattcg 60  
 acaccagatc actctttect ctaccacag gcttgctatg agcaagagac acaacctcct 120  
 ctcttctgtg ttccagcttc ttttctggtt cttcccaccc cttaagttct attcctgggg 180  
 atagagacac caatacccat aacctctctc ctaagcctcc ttataaccca ggggtgcacag 240  
 cacagactcc tgacaactgg taaggccaat gaactgggag ctcacagctg gctgtgcctg 300  
 a 301

<210> 267  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 267  
 aaagagcaca ggccagctca gcctgccctg gccatctaga ctcagcctgg ctccatgggg 60  
 gttctcagtg ctgagtcctat ccaggaaaag ctcacctaga cttcttgagg ctgaatcttc 120  
 atcctcacag gcagcttctg agagcctgat attcctagcc ttgatgggtc ggagtaaagc 180  
 ctcattctga ttctctcct tcttttctt caagttggct ttctcacaat ccctctgttc 240  
 aattcgcttc agcttgctctg ctttagccct catttcaga agcttcttct ctttggcctc 300  
 t 301

<210> 268  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 268  
 aatgtctcac tcaactactt ccagcctac cgtggcctaa ttctgggagt tttcttctta 60  
 gatcttggga gagctggttc ttctaaggag aaggaggaag gacagatgta actttggatc 120  
 tgaagagga agtctaattg aagtaattag tcaacgggtc ttgtttagac tcttgggaata 180  
 tgctgggttg ctcagtgagc ctttttggag aaagcaagta ttattcttaa ggagtaacca 240  
 cttcccattg ttctactttc taccatcatc aattgtatat tatgtattct ttggagaact 300  
 a 301

<210> 269  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 269  
 taacaatata cactagctat ctttttaact gtccatcatt agcaccaatg aagattcaat 60  
 aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact 120  
 atagtacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta 180  
 cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta 240  
 tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc 300  
 t 301

<210> 270  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 270  
 cattgaagag cttttgcgaa acatcagaac acaagtgcct ataaaattaa ttaagcctta 60  
 cacaagaata catattcctt ttattttctaa ggagttaaac atagatgtag ctgatgtgga 120  
 gagcttgctg gtgcagtgc aattggataa cactattcat ggccgaattg atcaagtcaa 180  
 ccaactcctt gaactggatc atcagaagaa ggggtggtgca cgatatactg cactagataa 240  
 tggaccaacc aactaaattc totcaccagg ctgtatcagt aaactggcct aacagaaaac 300  
 a 301

<210> 271  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 271  
 aaaaggttct cataagatta acaatttaaa taaatatttg atagaacatt cttttctcatt 60  
 tttatagctc atcttttagg ttgatattca gttcatgctt cccttgctgt tcttgatcca 120  
 gaattgcaat cacttcatca gcctgtattc gctccaattc tctataaagt gggccaagg 180  
 tgaaccacag agccacagca cacctctttc ccttggtgac tgccttcacc ccattganggt 240  
 tctctcctcc agatganaac tgatcatgag cccacatttt gggttttata gaagcagtca 300  
 c 301

<210> 272  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 272  
 taaattgcta agccacagat aacaccaatc aatggaaca aatcactgtc ttcaaagtgc 60  
 ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga 120  
 tccaataatt ccctcatgat gagcaagaaa aattctttgc gcaccctcc tgcattccaca 180  
 gcatcttctc caacaaatat aaccttgagt ggcttctgt aatctatgtt ctttgttttc 240  
 ctaaggactt ccattgcato tcctacaata ttttctctac gcaccactag aattaagcag 300  
 g 301

<210> 273  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>



<221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 273

acatgtgtgt atgtgtatct ttgggaaan aanaagacat cttgtttayt atttttttgg	60
agagangctg ggacatggat aatcacwtaa ttgtctayta tyactttaat ctgactygaa	120
gaaccgtcta aaaataaaat ttaccatgtc dtatattcct tatagtatgc ttatttcacc	180
ttytttctgt ccagagagag tatcagtgac ananatttma gggatgaamac atgmattggg	240
gggacttnty tttaacngagm accctgcccg sgccgcccgc makcngantt ccgcsananc	300
t	301

<210> 274  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 274

cttatatact ctttctcaga ggcaaaagag gagatgggta atgtagacaa ttcttttgagg	60
aacagtaaatt gattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa	120
tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttggt gaaaagtcga	180
tctaggtatg gttgcattct cgtcttctt tctgcagtag ataatgaggt aaccgaaggc	240
aattgtgctt cttttgataa gaagctttct tggatcatatc aggaaattcc aganaaaagtc	300
c	301

<210> 275  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 275

tccgtgtcag cagcacgtgg cattgaacat tgcaatgtgg agcccaaacc acagaaaatg	60
gggtgaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc	120
tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtgag	180
tcaagagact cccaggcctc agcgtacctg cccgggcggc cgctcgaagc cgaattctgc	240
agatatccat cacactggcg gncgctcgan catgcatcta gaaggnccaa ttcgccctat	300
a	301

<210> 276  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 276

tgtacacata ctcaataaat aaatgactgc attgtggtat tattactata ctgattatat	60
ttatcatgtg acttctaatt agaaaatgta tccaaaagca aaacagcaga tatcaaaat	120
taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc	180
caatacattt aaacattttgg gaaatgaggg ggacaaaatgg aagccagatc aaatttgtgt	240

aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggetctcctt caatggggat 300  
g 301

<210> 277  
<211> 301  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 277  
tttgttgatg tcagtattttt attacttgcg ttatgagtgc tcacctggga aattctaaag 60  
atacagaggaa cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg 120  
gaatcatggc actcctgata ctttcccaaa tcaacactct caatgccccca ccctcgtcct 180  
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga 240  
gttcnctgtc gattacatct gaccagtctc ctttttccga agtcctntccg ttcaatcttg 300  
c 301

<210> 278  
<211> 301  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 278  
taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat 60  
aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca 120  
cagtctctac tgttattatg cattacctgg gaatttatat aagcccttaa taataatgcc 180  
aatgaacatc tcatgtgtgc tcacaatggt ctgggactat tataagtgtc tcacagggtt 240  
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt 300  
c 301

<210> 279  
<211> 301  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 279  
aaagcaggaa tgacaaagct tgccttttctg gtatgttcta ggtgtattgt gacttttact 60  
gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc 120  
ttagaccttt accttccagc caccacacag tgccttgatat ttcagagtca gtcattgggt 180  
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac 240  
catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag 300  
a 301

<210> 280

<211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 280  
 ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg 60  
 tagaaagggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct 120  
 tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg 180  
 gtttgatata gtttaggggtt ggggttagat taagatctaa attacatcag gacaaagaga 240  
 cagactatta actccacagt taattaagga ggtatgttcc atgtttattt gttaaagcag 300  
 t 301

<210> 281  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 281  
 aggtacaaga aggggaatgg gaaagagctg ctgctgtggc attgttcaac ttggatattc 60  
 gccgagcaat ccaaattcctg aatgaagggg catcttctga aaaaggagat ctgaatctca 120  
 atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa 180  
 tgtgtagcac actgcgatta cagctaaata acccgatttt gtgtgtcatg tttgcatttc 240  
 tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagtt gcagtacctc 300  
 g 301

<210> 282  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 282  
 caggctactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca 60  
 tccagaaccc aaaaattaaag aaattcaaaa agacattttg tgggcacctg ctagcacaga 120  
 agcgagagaag caaagcccag gcagaacat gctaacctta cagctcagcc tgcacagaag 180  
 cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg 240  
 cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac agaagcacag 300  
 a 301

<210> 283  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 283  
 atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag 60  
 cacttttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca 120  
 gtgcactctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc 180  
 acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat gcatctttta 240  
 ggaaacatat acatttttta aaatctattt tatgtaagaa ctgacagacg aatttgcttt 300  
 g 301

<210> 284  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 284  
 caggtaaaaa acgctattaa gtggcttaga atttgaacat ttgtggtctt tatttacttt 60

```

gcttcgtgtg tgggcaaagc aacatcttcc ctaaatatat attaccaaga aaagcaagaa 120
gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat 180
ggtgagaggc aaggcatgag agggcaagtt tgttgtggac agatctgtgc ctactttatt 240
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaqaatt 300
a 301

```

```

<210> 285
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 285
acatcaccat gatcggtacc cccacccatt atacgttgta tgtttacata aatactcttc 60
aatgatcatt agtgttttaa aaaaaatact gaaaactcct tctgcatccc aatctctaac 120
caggaaagca aatgctatct acagacctgc aagccctccc tcaaacnaaa ctatttctgg 180
attaaatatg tctgacttct tttagagtca cagcactagg caaatgctat ttacgatctg 240
caaaagctgt ttgaagagtc aaagccccc a t t t t c t g g a c c o c t g t a a c a g 300
t 301

```

```

<210> 286
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 286
taccactgca ttccagcctg ggtgacagag tgagactccg tctccaaaaa aaactttgct 60
tgtatattat ttttgcctta cagtggatca ttctagtagg aaaggacagt aagatttttt 120
atcaaaatgt gtcattgccag taagagatgt tatattcttt tctcatttct tccccacca 180
aaaataagct accatatagc ttataagtct caaatttttg ctttttacta aaatgtgatt 240
gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt ttttcccttg 300
t 301

```

```

<210> 287
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 287
tacagatctg ggaactaaat attaaaaatg agtgtggctg gatatatgga gaatgttggg 60
cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg 120
aaatgatttg gttatgaacg cacagtttag gcagcagggc cagaatcctg accctctgcc 180
ccgtgggttat ctctcccca gcttggctgc ctcatgttat cacagtattc ctttttgttt 240
gttgcattgtc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc 300
t 301

```

```

<210> 288
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 288
gtacacctaa ctgcaaggac agctgaggaa tgtaatgggc agccgctttt aaagaagtag 60
agtcaatagg aagacaaatt ccagttccag ctcaagtctg gtatctgcaa agctgcaaaa 120

```

```

gatcttttaa gacaatttca agagaatatt tccttaaagt tggcaatttg gagatcatatc 180
aaaagcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag 240
tctgccttaa ttttgatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaa 300
a 301

```

```

<210> 289
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 289
ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgtctc tggaaactta 60
gcttttgatg tctccaagta gtccaccttc atttaactct ttgaaactgt atcatctttg 120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa 180
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggcggcgaan aagagaaaaga 240
tgtgttttgt tttggactct ctgtgtcccc ttccaatgct gtgggtttcc aaccagnnga 300
a 301

```

```

<210> 290
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 290
acactgagct cttcttgata aatatacaga atgcttggca tatacaagat tctatactac 60
tgactgatct gttcatttct ctcacagctc ttaccccaa aagcttttcc accctaagtg 120
ttctgacctc cttttctaata cacagtaggg atagaggcag anccacctac aatgaacatg 180
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctagcagtgc 240
tgccttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagtgag 300
a 301

```

```

<210> 291
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 291
caggtaccaa tttcttctat cctagaaaca tttcatttta tgttgttgaa acataacaac 60
tatatcagct agattttttt tctatgcttt acctgctatg gaaaatttga cacattctgc 120
tttactcttt tgtttatagg tgaatcacia aatgtatttt tatgtattct gtagttcaat 180
agccatggct gtttacttca ttttaatttat ttagcataaa gacattatga aaaggcctaa 240
acatgagctt cacttcccca ctaactaatt agcatctgtt atttcttaac cgtaatgctt 300
a 301

```

```

<210> 292
<211> 301
<212> DNA
<213> Homo sapien

```

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 292  
 accttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc 60  
 tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat gttgggtattc 120  
 aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg 180  
 ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc 240  
 tcactacaca cacagacccc acagtcctat atgccacaaa cacatttcca taacttgaaa 300  
 a 301

<210> 293  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 293  
 ggtaccaagt gctgggtgcc gctgtttacc tgtttctcact gaaaagtctg gctaagtctc 60  
 ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcctagagc actgactgtt 120  
 aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgtttctgt 180  
 gtgagaattt tttaaaaggc tactttgtata ataacccttg tcattttttaa tgtacctcgg 240  
 ccgcgaccac gctaagccga attctgcaga tatccatcac actggcggcc gctcgagcat 300  
 g 301

<210> 294  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 294  
 tgacccataa caatatacac tagctatctt ttttaactgtc catcattagc accaatgaag 60  
 attcaataaa attaccttta ttcacacatc tcaaaacaat tctgcaaatt cttagtgaag 120  
 ttttaactata gtcacaganc ttaaattatt acattgtttt ctatgtctac tgaaaataag 180  
 ttcactactt ttctgggata ttcttttcaa aatcttatta aaattcctgg tattatcacc 240  
 cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagaggt 300  
 t 301

<210> 295  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 295  
 gtactctttc tctccctccc tctgaattta attctttcaa cttgcaattt gcaaggatta 60  
 cacatttcac tgtgatgtat attgtgttgc aaaaaaaaaa gtgtctttgt ttaaaattac 120  
 ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga 180  
 actggtagaa aaacrtctga agagctagtc tatcagcatc tgacagggtga attggatggt 240  
 tctcagaacc atttcacca gacagcctgt ttctatcctg ttttaataaat tagtttgggt 300  
 tctct 305

<210> 296  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 296  
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 cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg 120  
 attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac 180  
 tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt 240  
 tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg 300  
 c 301

<210> 297  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(300)  
 <223> n = A,T,C or G

<400> 297  
 actgagtttt aactggacgc caagcaggca aggctggaag gttttgctct ctttgtgcta 60  
 aaggttttga aaaccttgaa ggagaatcat ttgacaaga agtacttaag agtctagaga 120  
 acaaagangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt 180  
 tccatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtggtc 240  
 accgcacctc ggccgcgacc acgctaagcc gaattctgca gatatccatc acactggcgg 300

<210> 298  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 298  
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 ggcattctgag agacctggtg ttccagtgtt tctggaaatg ggtcccagtg ccgccggctg 120  
 tgaagctctc agatcaatca cgggaagggc ctggcggttg tggccacctg gaaccaccct 180  
 gtccctgtctg ttacatttc actaycaggt tttctctggg cattacnatt tgttccccta 240  
 caacagtgc ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctccagcgagg 300  
 t 301

<210> 299  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 299  
 gttttgagac ggagtttcac tcttgttgcc cagactggac tgcaatggca gggctctctgc 60  
 tcactgcacc ctctgcctcc caggttcgag caattctcct gcctcagcct cccaggtagc 120  
 tgggattgca ggtcacgcc accataccca gctaattttt ttgtattttt agtagagacg 180  
 gagtttcgcc atgttggcca gctgggtctca aactcctgac ctcaagcgac ctgcctgcct 240

cggcctccca aagtgtgga attataggca tgagtcaaca cgcccagcct aaagatattt 300  
t 301

<210> 300  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 300  
attcagtttt atttgctgcc ccagtatctg taaccaggag tgccacaaaa tcttgccaga 60  
tatgtcccac acccactggg aaaggctccc acctggctac ttcctctatc agctgggtca 120  
gctgcattcc acaaggttct cagcctaatt agtttacta cctgccagtc tcaaaactta 180  
gtaaagcaag accatgacat tccccacgg aaatcagagt ttgcccacc gtcttggtac 240  
tataaagcct gcctctaaca gtccttgctt cttcacacca atcccagcgc catcccccat 300  
g 301

<210> 301  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 301  
ttaaattttt gagaggataa aaaggacaaa taatctagaa atgtgtcttc ttcagtctgc 60  
agaggacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggt 120  
gggaactcac aaagaccctc agagctgaga caccacaac agtgggagct cacaaagacc 180  
ctcagagctg agacaccac aacagtggga gctcacaag accctcagag ctgagacacc 240  
cacaacagca cctcgttcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt 300  
t 301

<210> 302  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 302  
aggtagacat ttagcttgtg gtaaatgact cacaaaactg attttaaaat caagttaatg 60  
tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac 120  
ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg 180  
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca 240  
caggatttga gatgctaagg cccagagat cgtttgatcc aaccctotta ttttcagagg 300  
g 301

<210> 303  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 303  
aggtagcaac tgtggaaata ggtagaggat cattttttct ttccatatca actaagttgt 60  
atattgtttt ttgacagttt aacacatctt cttctgtcag agattctttc acaatagcac 120  
tggctaattg aactaccgct tgcatgttaa aaatgggtgt ttgtgaaatg atcataggcc 180  
agtaacgggt atgtttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc 240  
catcgatttt atatctgggg tctagaaaag gagttaatct gttttccctc ataaattcac 300  
c 301

<210> 304  
<211> 301  
<212> DNA



<213> Homo sapien

<400> 304

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acatggatgt tattttgcag actgtcaacc tgaatttgta tttgcttgac attgcctaata 60
tattagtttc agtttcagct taccactttt ttgtctgcaa catgcaraas agacagtgcc 120
cttttttagtg tatcatatca ggaatcatct cacattgggt tgtgccatta ctgggtgcagt 180
gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga 240
ttttcctttt gtaattaata agtgtgtgtg tgaagattct ttgagatgag gtatataatct 300
c 301

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<210> 305

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1) ... (301)

<223> n = A,T,C or G

<400> 305

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gangtacagc gtgggtcaagg taacaagaag aaaaaaatgt gagtggcatc ctgggatgag 60
caggggggaca gacctggaca gacacgttgt catttgctgc tgtgggtagg aaaatgggag 120
taaaggagga gaaacagata caaaatctcc aactcagtat taaggatttc tcatgcctag 180
aatattggta gaaacaagaa tacattcata tggcaaataa ctaacatgg tggaacaaaa 240
ttctgggatt taagttggat accaangaaa ttgtattaaa agagctgttc atggaataag 300
a 301

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<210> 306

<211> 8

<212> PRT

<213> Homo sapien

<400> 306

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Val Leu Gly Trp Val Ala Glu Leu
1 5

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<210> 307

<211> 637

<212> DNA

<213> Homo sapien

<400> 307

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acagggratg aagggaaagg gagaggatga ggaagccccc ctggggattt ggtttggtcc 60
ttgtgatcag gtggtctatg gggcttatcc ctacaaagaa gaatocagaa ataggggcac 120
attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt 180
cacaccattg gtgagggagg gattaccacc ctgggggttat gaagatgggt gaacacccca 240
cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga 300
gcaggaggac gcttgacac catgcaggat gacatggggg atgcgctcgg gattggtgtg 360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga 420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtga 480
actcattagg ctgagaacct tgtggaatgc acttgaccca sctgatagag gaagtagcca 540
ggtgggagcc tttcccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg 600
ttacagatac tggggcagca aataaaaactg aatcttg 637

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<210> 308

<211> 647

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(647)

<223> n = A,T,C or G

<400> 308

acgattttca	ttatcatgta	aatcgggtca	ctcaaggggc	caaccacagc	tgggagccac	60
tgctcagggg	aaggttcata	tgggactttc	tactgcccac	ggttctatac	aggatataaa	120
ggngcctcac	agtatagatc	tggtagcaaa	gaagaagaaa	caaacactga	tctctttctg	180
ccacccctct	gaccctttgg	aactcctctg	accctttaga	acaagcctac	ctaatatctg	240
ctagagaaaa	gaccaacaac	ggcctcaaag	gatctcttac	catgaaggtc	tcagctaatt	300
cttgggtaag	atgtgggttc	cacattaggt	tctgaatatg	gggggaaggc	tcaatttgct	360
catttttgtg	gtggataaaag	tcaggatgcc	cagggggccag	agcagggggc	tgcttgcttt	420
gggaacaatg	gctgagcata	taaccatagg	ttatggggaa	caaaacaaca	tcaaagtcac	480
tgtatcaatt	gccatgaaga	cttgagggac	ctgaatctac	cgattcatct	taaggcagca	540
ggaccagttt	gagtggcaac	aatgcagcag	cagaatcaat	ggaaacaaca	gaatgattgc	600
aatgtccttt	ttttctcct	gcttctgact	tgataaaagg	ggaccgt		647

<210> 309

<211> 460

<212> DNA

<213> Homo sapien

<400> 309

actttatagt	ttaggctgga	cattggaaaa	aaaaaaaaagc	cagaacaaca	tgtgatagat	60
aatatgattg	gctgcacact	tccagactga	tgaatgatga	acgtgatgga	ctattgtatg	120
gagcacatct	tcagcaagag	ggggaaatac	tcattcattt	tggccagcag	ttgtttgatc	180
accaaacatc	atgccagaat	actcagcaaa	ccttcttagc	tcttgagaag	tcaaagtcag	240
ggggaattta	ttcctggcaa	ttttaattgg	actccttatg	tgagagcagc	ggctaccagc	300
ctgggggtgg	ggagcgaacc	cgtcactagt	ggacatgcag	tggcagagct	cctggtaacc	360
acctagagga	atacacaggc	acatgtgtga	tgccaagcgt	gacacctgta	gcactcaaat	420
ttgtcttgtt	tttgtctttc	ggtgtgtaag	attcttaagt			460

<210> 310

<211> 539

<212> DNA

<213> Homo sapien

<400> 310

acgggactta	tcaaataaag	ataggaaaag	aagaaaactc	aaatattata	ggcagaaatg	60
ctaaagggtt	taaaatatgt	caggattgga	agaaggcatg	gataaagaac	aaagttcagt	120
taggaaagag	aaacacagaa	ggaagagaca	caataaaagt	cattatgtat	tctgtgagaa	180
gtcagacagt	aagatttgtg	ggaaatgggt	tggtttgttg	tatggtatgt	attttagcaa	240
taatctttat	ggcagagaaa	gctaaaatcc	tttagcttgc	gtgaatgatc	acttgctgaa	300
ttcctcaagg	taggcatgat	gaaggagggt	ttagaggaga	cacagacaca	atgaactgac	360
ctagatagaa	agccttagta	tactcagcta	ggaatagtga	ttctgagggc	acactgtgac	420
atgattatgt	cattacatgt	atggtagtga	tggggatgat	aggaaggaag	aacttatggc	480
atattttcac	ccccacaaa	gtcagttaaa	tattgggaca	ctaaccatcc	aggtcaaga	539

<210> 311

<211> 526

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

&lt;222&gt; (1)... (526)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 311

caaatttgag	ccaatgacat	agaattttac	aaatcaagaa	gcttattctg	gggccatttc	60
ttttgacgtt	ttctctaaac	tactaaagag	gcattaatga	tccataaatt	atattatcta	120
catttacagc	atttaaaatg	tggtcagcat	gaaatattag	ctacagggga	agctaaataa	180
attaaacatg	gaataaagat	ttgtccttaa	atataatcta	caagaagact	ttgatatttg	240
tttttcacaa	gtgaagcatt	cttataaagt	gtcataacct	ttttggggaa	actatgggaa	300
aaaatgggga	aactctgaag	ggttttaagt	atcttacctg	aagctacaga	ctccataacc	360
tctctttaca	gggagctcct	gcagccccta	cagaaatgag	tggttgagat	tcttgattgc	420
acagcaagag	cttctcatct	aaaccctttc	cctttttagt	atctgtgtat	caagtataaa	480
agttctataa	actgtagtnt	acttatttta	atccccaaag	cacagt		526

&lt;210&gt; 312

&lt;211&gt; 500

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)... (500)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 312

cctctctctc	cccaccccct	gactctagag	aactggggtt	tctcccagta	ctccagcaat	60
tcattttctga	aagcagttga	gccactttat	tccaaagtac	actgcagatg	ttcaaactct	120
ccattttctct	ttcccttcca	cctgccagtt	ttgctgactc	tcaacttgct	atgagtgtaa	180
gcattaagga	cattatgctt	cttcgattct	gaagacaggc	cctgctcatg	gatgactctg	240
gcttcttagg	aaaatatttt	tcttccaaaa	tcagtaggaa	atctaaactt	atccccctct	300
tgcatagtc	tagcagcttc	agacatttgg	ttaagaacct	atgggaaaaa	aaaaaatcct	360
tgctaagtgt	gtttcctttg	ttaaccanga	ttcttatttg	nctggtatag	aatatcagct	420
ctgaacgtgt	ggtaaagatt	tttgtgtttg	aatataggag	aaatcagttt	gctgaaaagt	480
tagtcttaat	tatctattgg					500

&lt;210&gt; 313

&lt;211&gt; 718

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)... (718)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 313

ggagatttgt	gtggtttgca	gccgagggag	accaggaaga	tctgcatggt	gggaaggacc	60
tgatgatata	gaggtgagaa	ataagaaagg	ctgctgactt	taccatctga	ggccacacat	120
ctgctgaaat	ggagataatt	aacatcacta	gaaacagcaa	gatgacaata	taatgtctaa	180
gtagtacat	gtttttgcac	atttccagcc	cttttaata	tccacacaca	caggaagcac	240
aaaaggaagc	acagagatcc	ctgggagaaa	tgcccggccg	ccatcttggg	tcacgatga	300
gcctcgccct	gtgcctgntc	ccgcttggtg	gggaaggaca	ttagaaaaatg	aattgatgtg	360
ttccttaaag	gatggcagga	aaacagatcc	tggtgtggat	atttatttga	acgggattac	420
agatttgaaa	tgaagtcaca	aagtgcagcat	taccaatgag	aggaaaacag	acgagaaaat	480
cttgatgggt	cacaagacat	gcaacaaaca	aaatggaata	ctgtgatgac	acgagcagcc	540
aactggggag	gagataccac	ggggcagagg	tcaggattct	ggccctgctg	cctaactgtg	600
cgttatacca	atcatttcta	tttctaccct	caaacaagct	gtngaataac	tgacttacgg	660
ttcttntggc	ccacattttc	atnatccacc	cntcntttt	aannttantc	caaantgt	718

<210> 314  
 <211> 358  
 <212> DNA  
 <213> Homo sapien

<400> 314  
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 cataatcaaa tatagctgta gtacatgttt tcattgggtgt agattaccac aaatgcaagg 120  
 caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg tgtagtccaa 180  
 gctctcggta gtccagccac tgtgaaacat gctcccttta gattaacctc gtggacgctc 240  
 ttgttgatt gctgaactgt agtgccctgt attttgett tgtctgtgaa ttctgttgct 300  
 tctggggcat ttccttgta tgcagaggac caccacacag atgacagaa tctgaatt 358

<210> 315  
 <211> 341  
 <212> DNA  
 <213> Homo sapien

<400> 315  
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 ataggtgatg atgaggacat ggaatgggcc cccaaggatg gtctgtccaa agaagcgagt 120  
 gacccccatt ctgaagatgt ctggaacctc taccagcagg atgatgatag ccccaatgac 180  
 agtcaccagc tccccgacca gccggatatc gtccttaggg gtcatgtagg ctctctgaag 240  
 tagcttctgc tgtaagaggg tggtgtcccg ggggctcgtg cggttattgg tctctgggctt 300  
 gagggggcgg tagatgcagc acatggtgaa gcagatgatg t 341

<210> 316  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 316  
 agactgggca agactcttac gccccacact gcaatttggt cttgttgccg tatccattta 60  
 tgtgggcctt tctcgagttt ctgattataa acaccactgg agcgatgtgt tgactggact 120  
 cattcagga gctctggttg caatattagt t 151

<210> 317  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 317  
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 atcttcattt atctctggcc ttaaccctgg ctctgaggc tgcggccagc agatcccagg 120  
 ccagggtctt gttcttgcca cactgcttg a 151

<210> 318  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 318  
 actggtggga ggcgctgttt agttggctgt ttccagaggg gtctttcgga gggacctcct 60  
 gctgcaggct ggagtgtctt tattcctggc gggagaccgc acattccact gctgaggctg 120  
 tgggggcggg ttatcaggca gtgataaaca t 151

<210> 319

<211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 319  
 aactagtgga tccagagcta taggtacagt gtgatctcag ctttgcaaac acattttcta 60  
 catagatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg 120  
 taagattggg tttatgtgat tttagtgggt a 151

<210> 320  
 <211> 150  
 <212> DNA  
 <213> Homo sapien

<400> 320  
 aactagtgga tccactagtc cagtgtgggt gaattccatt gtgttggggt tctagatcgc 60  
 gagggtgc cttttttttt tttttttttg ggggggaatt tttttttttt aatagttatt 120  
 gagtgttcta cagcttacag taaataccat 150

<210> 321  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 321  
 agcaactttg tttttcatcc aggttatattt aggccttagga tttcctctca cactgcagtt 60  
 taggggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg 120  
 tgcctctgag aatcaaagt cttcatacac t 151

<210> 322  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(151)  
 <223> n = A,T,C or G

<400> 322  
 atccagcadc ttctcctggt tcttgccctc ctttttcttc ttcttasatt ctgcttgagg 60  
 ttggtggttg gtcagtttgc cacagggctt ggagatgggt acagtcttct ggcattcggc 120  
 attgtgcagg gctcgttca nacttcagt t 151

<210> 323  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(151)  
 <223> n = A,T,C or G

<400> 323  
 tgaggacttg tktttttttt cttttttttt aatcctctta ckttgtaaata atattgccta 60  
 nagactcant tactaccag tttgtggtt twtgggagaa atgtaactgg acagttagct 120  
 gttcaatyaa aaagacactt ancccatgtg g 151

<210> 324  
 <211> 461  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(461)  
 <223> n = A, T, C or G

<400> 324  
 acctgtgtgg aatttcagct ttcctcatgc aaaaggattt tgtatcccg gcctacttga 60  
 agaagtggc agctaaagga atccagggtt ttggttggac tgtaataacc tttgatgaaa 120  
 agagttacta cgaatcccat cttggttcca gctatatcac tgacagcatg gtagaagact 180  
 gcgaacctca cttctagact ttcacggtgg gacgaaacgg gtccagaaac tgccaggggc 240  
 ctcatacagg gatatacaaaa taccctttgt gctaccagg ccctggggaa tcagggtgact 300  
 cacacaaatg caatagttgg tcaactgcatt tttaccctgaa ccaaagctaa acccggtgtt 360  
 gccacatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga 420  
 aaaaacgcac aagagccct gccctgccct agctgangca c 461

<210> 325  
 <211> 400  
 <212> DNA  
 <213> Homo sapien

<400> 325  
 acactgtttc catgttatgt ttctacacat tgctacctca gtgctcctgg aaacttagct 60  
 tttgatgtct ccaagtagtc caccttcatt taactctttg aaactgtatc atctttgcc 120  
 agtaagagtg gtggcctatt tcagctgctt tgacaaaatg actggctcct gacttaacgt 180  
 tctataaatg aatgtgctga agcaaagtgc ccatggtggc ggcgaagaag agaaagatgt 240  
 gttttgtttt ggactctctg tggctccctc caatgctgtg gggttccaac caggggaagg 300  
 gtcccttttg cattgccaaag tgccataacc atgagcacta cgctaccatg gttctgctc 360  
 ctggccaagc aggtctggtt gcaagaatga aatgaatgat 400

<210> 326  
 <211> 1215  
 <212> DNA  
 <213> Homo sapien

<400> 326  
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 <212> PRT  
 <213> Homo sapien

<400> 327  
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 35 40 45  
 Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu  
 50 55 60  
 Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala  
 65 70 75 80  
 Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp  
 85 90 95  
 Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn  
 100 105 110  
 Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro  
 115 120 125  
 Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys  
 130 135 140  
 Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly  
 145 150 155 160  
 Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro  
 165 170 175  
 Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala  
 180 185 190  
 Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys  
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 210 215 220

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 <211> 234  
 <212> DNA  
 <213> Homo sapien

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 atccgcagtg ggtgctgtca gccacacact gtttcagaa ctctacacc atcgggctgg 180  
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 <213> Homo sapien

<400> 329  
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105

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20	25	30	
Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr			
35	40	45	
His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu			
50	55	60	
Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala			
65	70	75	

&lt;210&gt; 330

&lt;211&gt; 70

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 330

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&lt;210&gt; 331

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 331

Gln His Asn Gly Pro Ile Pro Ser Leu Thr Pro Pro Ser Gly Ser Leu		
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Val Ser Gly Ser Cys Ser		15
20		

&lt;210&gt; 332

&lt;211&gt; 2507

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 332

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&lt;211&gt; 3030

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 333

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&lt;210&gt; 334

&lt;211&gt; 2417

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 334

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&lt;211&gt; 2984

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 335

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```

tctttacatt tcttttaaaa taagcattta gtgctcagtc cctactgagt actctttctc 2520
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cacccccacc aaactttatt tttctatgtg ttttttgcaa catatgagtg ttttgaaaat 2940
aaagtaccca tgtctttatt agaaaaaaaa aaaaaaaaaa aaaa 2984

```

&lt;210&gt; 336

&lt;211&gt; 147

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 336

```

Pro Ser Phe Pro Thr Leu Leu Ser Arg Arg His Leu Gly Ser Tyr Leu
1          5          10          15
Leu Asp Ser Glu Asn Thr Ser Gly Ala Leu Pro Arg Leu Pro Gln Thr
20          25          30
Pro Lys Gln Pro Gln Lys Arg Ser Arg Ala Ala Phe Ser His Thr Gln
35          40          45
Val Ile Glu Leu Glu Arg Lys Phe Ser His Gln Lys Tyr Leu Ser Ala
50          55          60
Pro Glu Arg Ala His Leu Ala Lys Asn Leu Lys Leu Thr Glu Thr Gln
65          70          75          80
Val Lys Ile Trp Phe Gln Asn Arg Arg Tyr Lys Thr Lys Arg Lys Gln
85          90          95
Leu Ser Ser Glu Leu Gly Asp Leu Glu Lys His Ser Ser Leu Pro Ala
100          105          110
Leu Lys Glu Glu Ala Phe Ser Arg Ala Ser Leu Val Ser Val Tyr Asn
115          120          125
Ser Tyr Pro Tyr Tyr Pro Tyr Leu Tyr Cys Val Gly Ser Trp Ser Pro
130          135          140
Ala Phe Trp
145

```

&lt;210&gt; 337

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 337

```

Ala Leu Thr Gly Phe Thr Phe Ser Ala
1          5

```

&lt;210&gt; 338

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 338

```

Leu Leu Ala Asn Asp Leu Met L u Ile
1          5

```

&lt;210&gt; 339

&lt;211&gt; 318

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 339

```

Met Val Glu Leu Met Phe Pro Leu Leu Leu Leu Leu Leu Pro Phe Leu
 1      5      10      15
Leu Tyr Met Ala Ala Pro Gln Ile Arg Lys Met Leu Ser Ser Gly Val
 20      25      30
Cys Thr Ser Thr Val Gln Leu Pro Gly Lys Val Val Val Val Thr Gly
 35      40      45
Ala Asn Thr Gly Ile Gly Lys Glu Thr Ala Lys Glu Leu Ala Gln Arg
 50      55      60
Gly Ala Arg Val Tyr Leu Ala Cys Arg Asp Val Glu Lys Gly Glu Leu
 65      70      75      80
Val Ala Lys Glu Ile Gln Thr Thr Thr Gly Asn Gln Gln Val Leu Val
 85      90      95
Arg Lys Leu Asp Leu Ser Asp Thr Lys Ser Ile Arg Ala Phe Ala Lys
 100     105     110
Gly Phe Leu Ala Glu Glu Lys His Leu His Val Leu Ile Asn Asn Ala
 115     120     125
Gly Val Met Met Cys Pro Tyr Ser Lys Thr Ala Asp Gly Phe Glu Met
 130     135     140
His Ile Gly Val Asp His Leu Gly His Phe Leu Leu Thr His Leu Leu
 145     150     155     160
Leu Glu Lys Leu Lys Glu Ser Ala Pro Ser Arg Ile Val Asn Val Ser
 165     170     175
Ser Leu Ala His His Leu Gly Arg Ile His Phe His Asn Leu Gln Gly
 180     185     190
Glu Lys Phe Tyr Asn Ala Gly Leu Ala Tyr Cys His Ser Lys Leu Ala
 195     200     205
Asn Ile Leu Phe Thr Gln Glu Leu Ala Arg Arg Leu Lys Gly Ser Gly
 210     215     220
Val Thr Thr Tyr Ser Val His Pro Gly Thr Val Gln Ser Glu Leu Val
 225     230     235     240
Arg His Ser Ser Phe Met Arg Trp Met Trp Trp Leu Phe Ser Phe Phe
 245     250     255
Ile Lys Thr Pro Gln Gln Gly Ala Gln Thr Ser Leu His Cys Ala Leu
 260     265     270
Thr Glu Gly Leu Glu Ile Leu Ser Gly Asn His Phe Ser Asp Cys His
 275     280     285
Val Ala Trp Val Ser Ala Gln Ala Arg Asn Glu Thr Ile Ala Arg Arg
 290     295     300
Leu Trp Asp Val Ser Cys Asp Leu Leu Gly Leu Pro Ile Asp
 305     310     315

```

&lt;210&gt; 340

&lt;211&gt; 483

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 340

```

gccgaggtct gccttcacac ggaggacacg agactgcttc ctcaaggggt cctgcctgcc      60
tggacactgg tgggaggcgc tgtttagttg gctgttttca gaggggtctt tcggaggggac      120
ctcctgctgc aggctggagt gtctttattc ctggcgggag accgcacatt ccaactgctga      180
ggttggtggg gcggtttatc aggcagtgat aaacataaga tgtcattttcc ttgactccgg      240
ccttcaattt tctctttggc tgacgacgga gtccgtgggtg tcccgatgta actgaccct      300
gtccaaacg tgacatcact gatgctcttc tcgggggtgc tgatggcccg cttgggtcacg      360
tgctcaatct cgccattcga ctcttgctcc aaactgtatg aagacacctg actgcacgtt      420

```

ttttctgggc ttccagaatt taaagtgaag ggcagcactc ctaagctccg actccgatgc 480  
ctg 483

<210> 341  
<211> 344  
<212> DNA  
<213> Homo sapien

<400> 341  
ctgctgctga gtcacagatt tcattataaa tagcctccct aaggaaaata cactgaatgc 60  
tatttttact aaccattcta tttttataga aatagctgag agttttctaaa ccaactctct 120  
gctgccttac aagtattaaa tatttttact ctttccataa agagtagctc aaaatgatga 180  
attaatttaa taatttctga tgatggtttt atctgcagta atatgtatat catctattag 240  
aatttactta atgaaaaact gaagagaaca aaatttgtaa ccactagcac ttaagtactc 300  
ctgattctta acattgtctt taatgaccac aagacaacca acag 344

<210> 342  
<211> 592  
<212> DNA  
<213> Homo sapien

<400> 342  
acagcaaaaa agaaactgag aagcccaaty tgctttcttg ttaacatcca cttatccaac 60  
caatgtggaa acttcttata cttggttcca ttatgaagtt ggacaattgc tgctatcaca 120  
cctggcaggt aaaccaatgc caagagagt atggaaacca ttggcaagac tttgttgatg 180  
accaggattg gaattttata aaaatattgt tgatgggaag ttgctaaagg gtgaattact 240  
tccctcagaa gagtgtaaag aaaagtcaga gatgctataa tagcagctat ttttaattggc 300  
aagtgccact gtggaaagag ttcctgtgtg tgctgaagtt ctgaagggca gtcaaattca 360  
tcagcatggg ctgttttggtg caaatgcaaa agcacaggtc ttttagcat gctggctctc 420  
cccgtgtcct tatgcaaata atcgtcttct tctaaatttc tcttaggctt ctttttccaa 480  
agttcttctt ggtttgtgat gtcttttctg ctttccatta attctataaa atagtatggc 540  
ttcagccacc cactcttcgc cttagcttga ccgtgagtct cggctgccc tg 592

<210> 343  
<211> 382  
<212> DNA  
<213> Homo sapien

<400> 343  
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cttaattgtt gtggctttct ctccagcctc tcttaggagg ggtaatggtg gacttggcat 120  
cttgtaactc tcttttctcc tttcttcccc tttctctgcc cgcctttccc atctgtctgt 180  
agacttcttg attgtcagtc tgtgtcacat ccagtgattg ttttggttcc tgttcccttt 240  
ctgactgcc aaggggctca gaaccccagc aatcccttcc tttcactacc ttcttttttg 300  
ggggttagttg gaagggactg aaattgtggg gggaaggtag gaggcacatc aataaagagg 360  
aaaccaccaa gctgaaaaaa aa 382

<210> 344  
<211> 536  
<212> DNA  
<213> Homo sapien

<400> 344  
ctgggcctga agctgtaggg taaatcagag gcaggcttct gagtgatgag agtcctgaga 60  
caataggcca cataaacttg gctggatgga acctcacaat aagggtggtca cctcttgttt 120  
gtttaggggg atgccaagga taaggccagc tcagttatat gaagagaagc agaacaaaca 180  
agtctttcag agaaatggat gcaatcagag tgggatcccc gtcacatcaa ggtcacactc 240  
caccttcatg tgctgaatg gttgccaggt cagaaaaatc cacccttacc gagtgcggct 300

```

tcgaccctat atcccccgcc cgcgtccctt tctccataaa attcttctta gtagctatta 360
ccttcttatt atttgatcta gaaattgcc tctttttacc cctaccatga gccctacaaa 420
caactaacct gccactaata gttatgtcat ccctcttatt aatcatcatc ctagccctaa 480
gtctggccta tgagtgacta caaaaaggat tagactgagc cgaataacaa aaaaaa 536

```

&lt;210&gt; 345

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 345

```

accttttgag gtctctctca ccacctccac agccaccgtc accgtgggat gtgctggatg 60
tgaatgaagc ccccatcttt gtgcctcctg aaaagagagt ggaagtgtcc gaggactttg 120
gcgtgggcca ggaaatcaca tcctacactg ccaggagacc agacacattt atggaacaga 180
aaataacata tcggatttgg agagacactg ccaactggct ggagattaat ccggacactg 240
gtgccatttc c 251

```

&lt;210&gt; 346

&lt;211&gt; 282

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(282)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 346

```

cgcgtctctg aactgtgat catgacaggg gttcaaacag aaagtgcctg ggccctcctt 60
ctaagtcttg ttacacaaaaa aaggaaaaag aaaagatctt ctacgttaca aattctggga 120
agggagacta tacctggctc ttgccctaag tgagaggtct tccctccgc accaaaaaat 180
agaaaggctt tctatttcac tggcccagggt agggggaagg agagtaactt tgagtctgtg 240
ggtctcattt cccaagggtgc cttcaatgct catnaaaacc aa 282

```

&lt;210&gt; 347

&lt;211&gt; 201

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(201)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 347

```

acacacataa tattataaaa tgccatctaa ttggaaggag ctttctatca ttgcaagtca 60
taaataatac ttttaaaana ntactancag cttttacctt ngctcctaaa tgcttgtaaa 120
tctgagactg actggacca cccagacca gggcaaagat acatgttacc atatcatctt 180
tataaagaat tttttttgt c 201

```

&lt;210&gt; 348

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 348

```

ctgttaatca caacatttgt gcatcaactg tgccaagtga gaaaatgttc taaaatcaca 60
agagagaaca gtgccagaat gaaactgacc ctaagtccca ggtgccctg ggcaggcaga 120

```

aggagacact	cccagcatgg	aggaggggtt	atcttttcat	cctagggtcag	gtctacaatg	180
ggggaagggt	ttattataga	actccaaca	gccacctca	ctcctgccac	ccacccgatg	240
gccctgcctc	c					251

&lt;210&gt; 349

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 349

taaaaatcaa	gccatttaaat	tgtatctttg	aaggtaaqaca	atatatggga	gctggatcac	60
aaccctgag	gatgccagag	ctatgggtcc	agaacatggg	gtgggtattat	caacagagtt	120
cagaagggtc	tgaactctac	gtgttaccag	agaacataat	gcaattcatg	cattccactt	180
agcaattttg	taaaatacca	gaaacagacc	ccaagagtct	ttcaagatga	ggaaaattca	240
actcctgggt	t					251

&lt;210&gt; 350

&lt;211&gt; 908

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 350

ctggacactt	tgcgagggtc	tttgctggct	gctgctgctg	cccgtcatgc	tactcatcgt	60
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cggttggaat	tgctctgggt	atgatgacag	agaaaatgat	ctcttcctct	gtgacaccaa	180
cacctgtaaa	tttgatgggg	aatgtttaag	aattggagac	actgtgactt	gcgtctgtca	240
gttcaagtgc	aacaatgact	atgtgcctgt	gtgtgggtcc	aatggggaga	gctaccagaa	300
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aggatcatgt	gccacagtcc	atgaaggctc	tggagaaact	agtcaaaagg	agacatccac	420
ctgtgatatt	tgccagtttg	gtgcagaatg	tgacgaagat	gccgaggatg	tctgggtgtg	480
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ccacatacct	tgtccggaac	attacaatgg	cttctgcatg	catgggaagt	gtgagcattc	780
tatcaatatg	caggagccat	cttgccaggtg	tgatgctggg	tatactggac	aacactgtga	840
aaaaaaggac	tacagtgttc	tatacgttgt	tcccggctct	gtacgatttc	agtatgtctt	900
aatcgacg						908

&lt;210&gt; 351

&lt;211&gt; 472

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 351

ccagttatatt	gcaagtggta	agagcctatt	taccataaat	aataactaaga	accaactcaa	60
gtcaaacctt	aatgccattg	ttattgtgaa	ttaggattaa	gtagtaattt	tcaaaattca	120
cattaacttg	atttttaaat	cagwtttgyg	agtcatttac	cacaagctaa	atgtgtacac	180
tatgataaaa	acaaccattg	tattcctggt	tttctaaca	gtcctaattt	ctaactgt	240
atatatcctt	gcacatcaat	gaactttggt	ttcttttact	ccagtaataa	agtaggcaca	300
gatctgtcca	caacaaaactt	gccctctcat	gccttgctc	tcaccatgct	ctgctccagg	360
tcagccccct	tttggcctgt	ttgttttgc	aaaaacctaa	tctgcttctt	gcttttcttg	420
gtaatatata	tttagggaag	atgttgcttt	gccacacac	gaagcaaagt	aa	472

&lt;210&gt; 352

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien



## &lt;400&gt; 352

ctcaaagcta	atctctcggg	aatcaaacca	gaaaagggca	aggatcttag	gcattggtgga	60
tgtggataag	gccaggtcaa	tggctgcaag	catgcagaga	aagaggtaca	tcggagcgtg	120
caggtgcgt	tccgtcctta	cgatgaagac	cacgatgcag	tttccaaaca	ttgccactac	180
atacatggaa	aggaggggga	agccaaccca	gaaatgggct	ttctctaate	ctgggatacc	240
aataagcaca	a					251

## &lt;210&gt; 353

## &lt;211&gt; 436

## &lt;212&gt; DNA

## &lt;213&gt; Homo sapien

## &lt;400&gt; 353

tttttttttt	tttttttttt	tttttttaca	caatgcagtc	atatttttat	tgagtatgtg	60
cacattatgg	tattattact	atactgatta	tatttatcat	gtgacttcta	attaraaaat	120
gtatccaaaa	gcaaaacagc	agatatataa	aattaaagag	acagaagata	gacattaaca	180
gataaggcaa	cttatacatt	gacaatccaa	atccaatata	tttaaacatt	tgggaaatga	240
gggggacaaa	tggaagccar	atcaaatttg	tgtaaaacta	ttcagtatgt	ttcccttgct	300
tcatgtctga	raaggctctc	cottcaatgg	ggatgacaaa	ctccaaatgc	cacacaaatg	360
ttaacagaat	actagattca	cactggaacg	ggggtaaaga	agaaattatt	ttctataaaa	420
gggctcctaa	tgtagt					436

## &lt;210&gt; 354

## &lt;211&gt; 854

## &lt;212&gt; DNA

## &lt;213&gt; Homo sapien

## &lt;400&gt; 354

ccttttctag	ttcaccagtt	ttctgcaagg	atgctgggta	gggagtgtct	gcaggaggag	60
caagtctgaa	accaaatcta	ggaaacatag	gaaacgagcc	aggcacaggg	ctgggtgggccc	120
atcaggggacc	accctttggg	ttgatatttt	gcttaatctg	catcttttga	gtaagatcat	180
ctggcagtag	aagctgttct	ccaggtacat	ttctctagct	catgtacaaa	aacatcctga	240
aggactttgt	caggtgcctt	gctaaaagcc	agatgcgttc	ggcacttcc	tgggtctgagg	300
ttaattgcac	acctacaggg	actgggctca	tgctttcaag	tattttgtcc	tcacttttagg	360
gtgagtga	gatccccatt	ataggagcac	ttgggagaga	tcataataaa	gctgactctt	420
gagtacatgc	agtaatgggg	tagatgtgtg	tgggtgtgtc	tcattcctgc	aagggtgctt	480
gttagggagt	gtttccagga	ggaacaagtc	tgaaccat	catgaaataa	atggtagggtg	540
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caatatggaa	ggctctaatt	tgcccatatt	tgaataata	attcagcttt	ttgtaataca	660
aaataacaaa	ggattgagaa	tcattgtgtc	taattgtata	aagaccaggg	aaacataaat	720
atatcaactg	cataaatgta	aaatgcatgt	gacccaagaa	ggccccaag	tggcagacaa	780
cattgtaccc	attttccctt	ccaaaatgtg	agcggcgggc	ctgctgcttt	caaggctgtc	840
acacgggatg	tcag					854

## &lt;210&gt; 355

## &lt;211&gt; 676

## &lt;212&gt; DNA

## &lt;213&gt; Homo sapien

## &lt;400&gt; 355

gaaattaagt	atgagctaaa	ttccctgtta	aaacctctag	gggtgacaga	tctcttcaac	60
caggtcaaag	ctgatctttc	tggaaatgtca	ccaaccaagg	gcctatattt	atcaaaagcc	120
atccacaagt	catacctgga	tgtcagcgaa	gagggcacgg	aggcagcagc	agccactggg	180
gacgacatcg	ctgtaaaaag	cctaccaatg	agagctcagt	tcaaggcgaa	ccacccttcc	240
ctgttcttta	taaggcacac	tcataccaac	acgactctat	tctgtggcaa	gcttgccctc	300
ccctaatacag	atgggggtga	gtaagggtca	gagttgcaga	tgaggtgcag	agacaatcct	360
gtgactttcc	cacggccaaa	aagctgttca	cacctcacgc	acctctgtgc	ctcagtttgc	420

tcatctgcaa	aataggtcta	ggatttcttc	caaccatttc	atgagttgtg	aagctaaggc	480
tttgtttaac	atggaaaaag	gtagacttat	gcagaaagcc	tttctggctt	tcttatctgt	540
ggtgtctcat	ttgagtgtctg	tccagtgaca	tgatcaagtc	aatgagtaaa	attttaaggg	600
attagatttt	cttgacttgt	atgtatctgt	gagatcttga	ataagtgacc	tgacatctct	660
gcttaaagaa	aaccag					676

<210> 356  
 <211> 574  
 <212> DNA  
 <213> Homo sapien

<400> 356						
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catgtggcac	ctgactggca	tcaaaccaaa	gttcgtaggc	caacaaagat	gggccactca	120
caagcttccc	atttgtagat	ctcagtgccct	atgagtatct	gacacctgtt	cctctcttca	180
gtctcttagg	gaggcttaaa	totgtctcag	gtgtgctaag	agtgccagcc	caaggkggtc	240
aaaagtccac	aaaactgcag	tctttgctgg	gatagtaagc	caagcagtgc	ctggacagca	300
gagttctttt	cttgggcaac	agataaccag	acaggactct	aatcgtgctc	ttattcaaca	360
ttcttctgtc	tctgcctaga	ctggaataaa	aagccaatct	ctctcgtggc	acaggggaagg	420
agatacaagc	togtttacat	gtgatagatc	taacaaaggc	atctaccgaa	gtctgggtctg	480
gatagacggc	acagggagct	cttaggtcag	cgctgctggg	tggaggacat	tcctgagtc	540
agctttgcag	cctttgtgca	acagtacttt	ccca			574

<210> 357  
 <211> 393  
 <212> DNA  
 <213> Homo sapien

<400> 357						
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aagccacaac	caaracttga	ttttatcaac	aaaaaccctt	aaatataaac	ggsaaaaaag	180
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araarataag	tgttatatgg	aaagaagggc	attcaagcac	actaaaraaa	cctgaggkaa	300
gcataatctg	tacaaaatta	aactgtcctt	tttggcattt	taacaaattt	gcaacgktct	360
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<210> 358  
 <211> 630  
 <212> DNA  
 <213> Homo sapien

<400> 358						
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gcatagagta	gggaagctaa	tccagcacag	ggaggtcaca	gagacatccc	taagggaagtg	180
gagtttaaac	tgagagaagc	aagtgtctaa	actgaaggat	gtgttgaaag	agaagggaga	240
gtagaacaat	ttgggcagag	ggaaccttat	agaccctaag	gtgggaaggt	tcaaagaact	300
gaaagagagc	tagaacagct	ggagccgttc	tccggtgtaa	agaggagtca	aagagataag	360
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gggtagactg	gactaggtaa	gactggaggc	aggtagacct	cttctaaggc	ctgcgatagt	540
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caagccagag	gttcctccac	aacaaccagt				630

<210> 359  
 <211> 620  
 <212> DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 359

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ctcaccagaa	gaataaagt	ctctgccagt	tattaaagga	ttactgctgg	tgaattaaat	180
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aggattaact	gttttaggaa	cagatataaa	gcttcgccac	ggaagagatg	gacaaagcac	300
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aacaaaaagc	tcacaccaa	caaaaccatc	aacttatitt	gtattctata	acatacgaga	600
ctgtaaagat	gtgacagtgt					620

&lt;210&gt; 360

&lt;211&gt; 431

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 360

aaaaaaaaaa	agccagaaca	acatgtgata	gataatatga	ttggctgcac	acttcagac	60
tgatgaatga	tgaacgtgat	ggactattgt	atggagcaca	tcttcagcaa	gagggggaaa	120
tactcatcat	ttttggccag	cagttgtttg	atcaccaaac	atcatgccag	aatactcagc	180
aaaccttctt	agctcttgag	aagtcaaagt	cggggggaat	ttattcctgg	caattttaat	240
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agtggacatg	cagtggcaga	gtccttggt	accacctaga	ggaatacaca	ggcacatgtg	360
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&lt;210&gt; 361

&lt;211&gt; 351

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 361

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&lt;210&gt; 362

&lt;211&gt; 463

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 362

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cgtaaaggat	ttccgcgtcc	gtgtcgcagg	acagacgtat	atacttccct	ttcttcccca	240
gtgtctcaaa	ctgaatatcc	ccaaaggcgt	cggtaggaaa	ttccttgggt	tgtttcttgt	300
agttccattt	ctcacttttg	ttgatctggg	tgcttccat	gtgctggctc	tgggcatagc	360
cacacttgca	cacattctcc	ctgataagca	cgatggtgtg	gacaggaagg	aaggatttca	420
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<210> 363  
 <211> 653  
 <212> DNA  
 <213> Homo sapien

<220>  
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 <223> n = A,T,C or G

<400> 363  
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 ggtctgcaca gttcatggag gctgcagatg aggccttgga tgctctggat gctgctgcag 420  
 ctgaggccga agcccgggct gaagcaagaa cccgcatggg aattggagat gaggtgtgt 480  
 ntgggccctg gagctgggat gacattgagt ttgagctgct gacctgggat gaggaaggag 540  
 attttgaga tcntgggtcc agaattccat ttacctctg gccagatac caccagaatg 600  
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 <212> DNA  
 <213> Homo sapien

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 aaaacaaggt ggatagatct agaattgtaa cattttaaga aaaccatagc atttgacaga 180  
 tgagaaagct caattataga tgcaaagtta taactaaact actatagtag taaagaaata 240  
 catttcacac cttcatata aattcactat cttggcttga ggcactccat aaaatgtatc 300  
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 aagtggatgc gcggaaaatg aaatcttctt caatagccca g 401

<210> 365  
 <211> 356  
 <212> DNA  
 <213> Homo sapien

<400> 365  
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 gactgtcacg atgtgtatag tacagtttga caagcctggg tccatacaga ccgctggaga 300  
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<210> 366  
 <211> 1851  
 <212> DNA  
 <213> Homo sapien

<400> 366  
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aagatacatc	aacattttgc	tcaagtagag	ggctgactat	acttgetgat	ccacaacata	360
cagcaagtat	gagagcagtt	cttccatata	tatccagcgc	atttaaattc	gcttttttct	420
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aaggtatgtc	ccttctatgc	ctgttttgct	gaggggttta	attctcgtgc	c	1851

&lt;210&gt; 367

&lt;211&gt; 668

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 367

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aaaaaaaa						668

&lt;210&gt; 368

&lt;211&gt; 1512

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 368

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&lt;210&gt; 369

&lt;211&gt; 1853

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 369

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&lt;210&gt; 370

&lt;211&gt; 2184

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 370

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&lt;210&gt; 371

&lt;211&gt; 1855

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)... (1855)

&lt;223&gt; n = A, T, C or G

&lt;400&gt; 371

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&lt;210&gt; 372

&lt;211&gt; 1059

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 372

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<210> 373  
 <211> 1155  
 <212> DNA  
 <213> Homo sapien

<400> 373

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<210> 374  
 <211> 2000  
 <212> DNA  
 <213> Homo sapien

<400> 374

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aaaaaaaaaa	aaaaaaaaaa					2000

&lt;210&gt; 375

&lt;211&gt; 2040

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 375

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&lt;210&gt; 376

&lt;211&gt; 329

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 376

Met Asp Ile Val Val Ser Gly Ser His Pro Leu Trp Val Asp Ser Ph

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Leu	His	Leu	Ala	Gly	Ser	Asp	Leu	Leu	Ser	Arg	Ser	Leu	Met	Ala	Glu
		20						25					30		
Glu	Tyr	Thr	Ile	Val	His	Ala	Ser	Phe	Ile	Ser	Cys	Ile	Ser	Ser	Ser
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Leu	Asp	Gly	Gln	Gly	Glu	Arg	Gln	Glu	Gln	Arg	Gly	His	Phe	Trp	Arg
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Pro	Gln	Arg	Leu	Leu	Cys	Glu	Asp	Ala	Trp	Glu	Gln	Glu	Val	Gln	Val
65					70					75					80
Val	Leu	Pro	Leu	Leu	Pro	Leu	Leu	Gln	Gly	Ser	Gly	Lys	Ser	Asn	Val
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Val	Ala	Trp	Gly	Asp	Tyr	Asp	Asp	Ser	Ala	Phe	Met	Asp	Pro	Arg	Tyr
			100					105					110		
His	Val	His	Gly	Glu	Asp	Leu	Asp	Lys	Leu	His	Arg	Ala	Ala	Trp	Trp
		115					120					125			
Gly	Lys	Val	Pro	Arg	Lys	Asp	Leu	Ile	Val	Met	Leu	Arg	Asp	Thr	Asp
	130					135					140				
Val	Asn	Lys	Arg	Asp	Lys	Gln	Lys	Arg	Thr	Ala	Leu	His	Leu	Ala	Ser
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Ala	Asn	Gly	Asn	Ser	Glu	Val	Val	Lys	Leu	Val	Leu	Asp	Arg	Arg	Cys
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Gln	Leu	Asn	Val	Leu	Asp	Asn	Lys	Lys	Arg	Thr	Ala	Leu	Thr	Lys	Ala
		180						185					190		
Val	Gln	Cys	Gln	Glu	Asp	Glu	Cys	Ala	Leu	Met	Leu	Leu	Glu	His	Gly
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Thr	Asp	Pro	Asn	Ile	Pro	Asp	Glu	Tyr	Gly	Asn	Thr	Thr	Leu	His	Tyr
	210					215					220				
Ala	Val	Tyr	Asn	Glu	Asp	Lys	Leu	Met	Ala	Lys	Ala	Leu	Leu	Leu	Tyr
225					230					235					240
Gly	Ala	Asp	Ile	Glu	Ser	Lys	Asn	Lys	His	Gly	Leu	Thr	Pro	Leu	Leu
			245						250					255	
Leu	Gly	Ile	His	Glu	Gln	Lys	Gln	Gln	Val	Val	Lys	Phe	Leu	Ile	Lys
		260					265						270		
Lys	Lys	Ala	Asn	Leu	Asn	Ala	Leu	Asp	Arg	Tyr	Gly	Arg	Thr	Ala	Leu
	275					280					285				
Ile	Leu	Ala	Val	Cys	Cys	Gly	Ser	Ala	Ser	Ile	Val	Ser	Pro	Leu	Leu
	290					295					300				
Glu	Gln	Asn	Val	Asp	Val	Ser	Ser	Gln	Asp	Leu	Glu	Arg	Arg	Pro	Glu
305					310					315					320
Ser	Met	Leu	Phe	Leu	Val	Ile	Ile	Met							
				325											

&lt;210&gt; 377

&lt;211&gt; 148

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(148)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 377

Met	Thr	Xaa	Pro	Ser	Trp	Ser	Pro	Gly	Thr	Thr	Ser	Val	Glu	Lys	Ile
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Trp	Thr	Ser	Ser	Thr	Glu	Leu	Pro	Trp	Trp	Gly	Lys	Val	Pro	Arg	Lys
		20					25					30			
Asp	Leu	Ile	Val	Met	Leu	Arg	Asp	Thr	Asp	Val	Asn	Lys	Xaa	Asp	Lys

125

35 40 45  
 Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu  
 50 55 60  
 Val Val Lys Leu Xaa Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp  
 65 70 75 80  
 Asn Lys Lys Arg Thr Ala Leu Xaa Lys Ala Val Gln Cys Gln Glu Asp  
 85 90 95  
 Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro  
 100 105 110  
 Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Xaa Tyr Asn Glu Asp  
 115 120 125  
 Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser  
 130 135 140  
 Lys Asn Lys Val  
 145

<210> 378  
 <211> 1719  
 <212> PRT  
 <213> Homo sapien

<400> 378  
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 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
 35 40 45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
 50 55 60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65 70 75 80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
 85 90 95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
 100 105 110  
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285

Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr  
 290 295 300  
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile  
 305 310 315 320  
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu  
 325 330 335  
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val  
 340 345 350  
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile  
 355 360 365  
 Ser Ser Glu Asn Ser Asn Pro Glu Asn Val Ser Arg Thr Arg Asn Lys  
 370 375 380  
 Pro Arg Thr His Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser  
 385 390 395 400  
 Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys  
 405 410 415  
 Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly  
 420 425 430  
 Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys  
 435 440 445  
 Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly  
 450 455 460  
 Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys  
 465 470 475 480  
 Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys  
 485 490 495  
 Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp  
 500 505 510  
 Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu  
 515 520 525  
 Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp  
 530 535 540  
 Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln  
 545 550 555 560  
 Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val  
 565 570 575  
 Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn  
 580 585 590  
 Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu  
 595 600 605  
 Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp  
 610 615 620  
 Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys  
 625 630 635 640  
 Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys  
 645 650 655  
 Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys  
 660 665 670  
 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala  
 675 680 685  
 Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly  
 690 695 700  
 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser  
 705 710 715 720  
 Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser  
 725 730 735  
 His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln  
 740 745 750

Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys  
 755 760 765  
 Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser  
 770 775 780  
 Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp  
 785 790 795 800  
 Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly  
 805 810 815  
 Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn  
 820 825 830  
 Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe  
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 Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser  
 850 855 860  
 Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn  
 865 870 875 880  
 Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu  
 885 890 895  
 Glu Gly Ser Glu Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile  
 900 905 910  
 Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn  
 915 920 925  
 Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro  
 930 935 940  
 Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu  
 945 950 955 960  
 Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe  
 965 970 975  
 Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His  
 980 985 990  
 Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser  
 995 1000 1005  
 Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu  
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 Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His  
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 Gln Ser Gln Leu Pro Arg Thr His Met Val Val Glu Val Asp Ser Met  
 1045 1050 1055  
 Pro Ala Ala Ser Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met  
 1060 1065 1070  
 Gly Lys Trp Cys Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys  
 1075 1080 1085  
 Ser Asn Val Gly Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr  
 1090 1095 1100  
 Leu Arg Ser Lys Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys  
 1105 1110 1115 1120  
 Arg Gly Ser Gly Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp  
 1125 1130 1135  
 Ser Ala Met Lys Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His  
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 Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp  
 1155 1160 1165  
 Gly Asp Tyr Asp Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg  
 1170 1175 1180  
 Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val  
 1185 1190 1195 1200  
 Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys  
 1205 1210 1215

Lys Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly  
 1220 1225 1230  
 Asn Ser Glu Val Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn  
 1235 1240 1245  
 Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys  
 1250 1255 1260  
 Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro  
 1265 1270 1275 1280  
 Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr  
 1285 1290 1295  
 Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp  
 1300 1305 1310  
 Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val  
 1315 1320 1325  
 His Glu Gln Lys Gln Gln Val Lys Phe Leu Ile Lys Lys Lys Ala  
 1330 1335 1340  
 Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala  
 1345 1350 1355 1360  
 Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn  
 1365 1370 1375  
 Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr  
 1380 1385 1390  
 Ala Val Ser Ser His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr  
 1395 1400 1405  
 Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu  
 1410 1415 1420  
 Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly  
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 Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn  
 1445 1450 1455  
 Lys Asp Gly Asp Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser  
 1460 1465 1470  
 Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly  
 1475 1480 1485  
 Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu  
 1490 1495 1500  
 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys  
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 Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser  
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 Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu  
 1540 1545 1550  
 Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser  
 1555 1560 1565  
 Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe  
 1570 1575 1580  
 Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe  
 1585 1590 1595 1600  
 Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly  
 1605 1610 1615  
 Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro  
 1620 1625 1630  
 Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln  
 1635 1640 1645  
 Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile  
 1650 1655 1660  
 Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser  
 1665 1670 1675 1680

Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn  
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 Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr  
 1700 1705 1710  
 Met Lys His Gln Ser Gln Leu  
 1715

<210> 379  
 <211> 656  
 <212> PRT  
 <213> Homo sapien

<400> 379  
 Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys  
 1 5 10 15  
 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe  
 20 25 30  
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
 35 40 45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
 50 55 60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65 70 75 80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
 85 90 95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
 100 105 110  
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285  
 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr  
 290 295 300  
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala S r Ile  
 305 310 315 320  
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu  
 325 330 335  
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val  
 340 345 350  
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile



355                      360                      365  
 Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu  
 370                      375                      380  
 Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys  
 385                      390                      395                      400  
 Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu  
                          405                      410                      415  
 Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn  
                          420                      425                      430  
 Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro  
                          435                      440                      445  
 Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu  
                          450                      455                      460  
 Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu  
 465                      470                      475                      480  
 Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp  
                          485                      490                      495  
 Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu  
                          500                      505                      510  
 Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys  
                          515                      520                      525  
 Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly  
                          530                      535                      540  
 Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser  
 545                      550                      555                      560  
 Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr  
                          565                      570                      575  
 His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln  
                          580                      585                      590  
 Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln  
                          595                      600                      605  
 Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys  
                          610                      615                      620  
 Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile  
 625                      630                      635                      640  
 Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu  
                          645                      650                      655

&lt;210&gt; 380

&lt;211&gt; 671

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 380

Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys  
 1                      5                      10                      15  
 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe  
                          20                      25                      30  
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
                          35                      40                      45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
                          50                      55                      60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65                      70                      75                      80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
                          85                      90                      95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
                          100                      105                      110

Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285  
 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr  
 290 295 300  
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile  
 305 310 315 320  
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu  
 325 330 335  
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His Val  
 340 345 350  
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile  
 355 360 365  
 Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu  
 370 375 380  
 Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys  
 385 390 395 400  
 Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu  
 405 410 415  
 Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn  
 420 425 430  
 Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro  
 435 440 445  
 Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu  
 450 455 460  
 Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu  
 465 470 475 480  
 Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp  
 485 490 495  
 Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu  
 500 505 510  
 Asn Gly Gln Pro Glu Lys Arg Ser Gln Glu Pro Glu Ile Asn Lys Asp  
 515 520 525  
 Gly Asp Arg Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys Lys  
 530 535 540  
 His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly Ala  
 545 550 555 560  
 Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser Arg  
 565 570 575

Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His  
 580 585 590  
 Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn  
 595 600 605  
 Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile  
 610 615 620  
 Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys Lys  
 625 630 635 640  
 Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala  
 645 650 655  
 Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu  
 660 665 670

&lt;210&gt; 381

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 381

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ggtaacatgc	ttcccctaag	ggtatcccaa	cccagggggc	tcacatgac	ctctgagggg	120
ccaatatccc	aggagaagca	ttggggagtt	gggggcaggt	gaaggaccca	ggactcacac	180
atcctggggc	tccaaggcag	aggagaggggt	cctcaagaag	gtcaggagga	aaatccgtaa	240
caagcagtca	g					251

&lt;210&gt; 382

&lt;211&gt; 3279

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 382

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cctcagtcct	tccctccac	tccatcctcc	atctggcctc	agtgggtcat	tctgatcact	660
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tgtttgtggg	gtgcagagat	gggagggggg	gggccacccc	tggaagagtg	gacagtgaca	1620

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tagccataga gattcacagc ccagagcagg aggacgtgc acaccatgca ggatgacatg 2940
ggggatgcgc tcgggatttg tgtgaagaag caaggactgt tagaggcagg ctttatagta 3000
acaagacggt ggggcaaact ctgatttccg tgggggaatg tcatggtctt gctttactaa 3060
gttttgagac tggcaggtag tgaaactcat taggctgaga acctgtgga atgcagctga 3120
cccagctgat agaggaagta gccagggtgg agcctttccc agtgggtgtg ggacatatct 3180
ggcaagattt tgtggcactc ctggttacag atactggggc agcaaataaa actgaatctt 3240
gttttcagac cttaaaaaaa aaaaaaaaaa aaaagtttt 3279

```

&lt;210&gt; 383

&lt;211&gt; 154

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 383

```

Met Ala Gly Val Arg Asp Gln Gly Gln Gly Ala Arg Trp Pro His Thr
          5                      10                      15

```

```

Gly Lys Arg Gly Pro Leu Leu Gln Gly Leu Thr Trp Ala Thr Gly Gly
          20                      25                      30

```

```

His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln
          35                      40                      45

```

```

Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
          50                      55                      60

```

```

Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly
          65                      70                      75                      80

```

```

Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
          85                      90                      95

```

```

Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
          100                     105                     110

```

```

Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
          115                     120                     125

```

Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn  
 130 135 140

Ala Leu Glu Arg Gly His Leu Val Arg Glu  
 145 150

<210> 384  
 <211> 557  
 <212> DNA  
 <213> Homo sapiens

<400> 384  
 ggatcctcta gagcggcgc ctactactac taaattcgcg gccgcgtcga cgaagaagag 60  
 aaagatgtgt tttgttttgg actctctgtg gtcccttcca atgctgtggg tttccaacca 120  
 ggggaagggt cccttttgc tggccaagt ccataaccat gagcactact ctaccatggg 180  
 tctgcctcct ggccaagcag gctggtttgc aagaatgaaa tgaatgattc tacagctagg 240  
 acttaacctt gaaatggaaa gtcttgcaat cccatttgc ggatccgtct gtgcacatgc 300  
 ctctgtagag agcagcattc ccagggacct tggaaacagt tggcactgta aggtgcttgc 360  
 tccccaaagac acatcctaaa aggtgttgta atggtgaaaa cgtcttccct ctttattgcc 420  
 ccttcttatt tatgtgaaca actgtttgtc tttttttgta tcttttttaa actgtaaagt 480  
 tcaattgtga aatgaatat catgcaaata aattatgcga ttttttttcc aaagtaaaaa 540  
 aaaaaaaaa aaaaaaa 557

<210> 385  
 <211> 337  
 <212> DNA  
 <213> Homo sapiens

<400> 385  
 ttcccagggt atgtgcgagg gaagacacat ttactatcct tgatggggct gattccttta 60  
 gtttctctag cagcagatgg gttaggagga agtgaccaa gtggttgact cctatgtgca 120  
 tctcaaagcc atctgctgtc ttcgagtacg gacacatcat cactcctgca ttgttgatca 180  
 aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240  
 tatcagacag gtccagtttc cgcaccaaca cctgctggtt ccctgtcgtg gtctggatct 300  
 ctttggccac caattcccc ttttccacat cccggca 337

<210> 386  
 <211> 300  
 <212> DNA  
 <213> Homo sapiens

<400> 386  
 gggcccgtcta ccggcccagg ccccgccctcg cgagtcctcc tccccgggtg cctgcccgcga 60  
 gcccgctcgg ccagaggggt gggcgcgggg ctgcctctac cggctggcgg ctgtaactca 120  
 gcgaccttgg ccgaaggct ctagcaagga ccaccgacc ccagccgcgg cggcgcgggc 180  
 gcggactttg ccggtgtgt gggcgggagc ggactgctg tccgcggacg ggcagcgaag 240  
 atgttagcct tcgctgccag gaccgtggac cgatcccagg gctgtggtgt aacctcagcc 300

<210> 387  
 <211> 537  
 <212> DNA  
 <213> Homo sapiens

<400> 387  
 gggccgagtc gggcaccaag ggactctttg caggcttctt tctcgggac atcaaggctg 60  
 cccctctctg tgccatcatg atcagcacct atgagttcgg caaaagcttc ttccagaggc 120

```

tgaaccagga cgggcttctg ggcggctgaa aggggcaagg aggcaaggac cccgtctctc 180
ccacggatgg ggagagggca ggaggagacc cagccaagtg ccttttctc agcactgagg 240
gagggggctt gtttcccttc cctcccgcg acaagctcca gggcagggct gtccctctgg 300
gcggcccagc acttcctcag acacaacttc ttctgctgc tccagtcgtg gggatcatca 360
cttaccacc cccaagttc aagaccaa atctccagctg ccccttctgt gtttccctgt 420
gtttgctgta gctgggcatg totccaggaa ccaagaagcc ctcagcctgg tgtagtctcc 480
ctgacccttg ttaattcctt aagtctaaag atgatgaact tcaaaaaaaa aaaaaa 537

```

&lt;210&gt; 388

&lt;211&gt; 520

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

```

aggataattt ttaaaccaat caaatgaaaa aaacaaacaa acaaaaaagg aaatgtcatg 60
tgagggttaa ccagtttgca ttccccta atgtggaaaa taaggaggact actcagcact 120
gtttgaagat tgccctctct acagcttctg agaattgtgt tatttcactt gccaaagtga 180
ggaccccttc cccaacatgc ccagcccac ccctaagcat ggtcccttgt caccaggcaa 240
ccaggaaact gctacttggt gacctacca gagaccagga gggtttggtt agctcacagg 300
acttccccca cccagaaga ttagcatccc atactagact cataactcaac tcaactaggc 360
tcatactcaa ttgatgggta ttagacaatt ccatttcttt ctggttatta taaacagaaa 420
atctttcttc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
atgaacttgt cttattttta tgggtgggtt ttttctggt 520

```

&lt;210&gt; 389

&lt;211&gt; 365

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 389

```

cgttgcccc gtttgacaga aggaaaggcg gagcttattc aaagtctaga gggagtggag 60
gagttaaggc tggatttcag atctgctgg ttccagccgc agtggtgccct ctgctcccc 120
aacgactttc caaataatct caccagcgcc ttccagctca ggcgtcctag aagcgtcttg 180
aagcctatgg ccagctgtct ttgtgttccc tctccccgc ctgtcctcac agctgagact 240
cccaggaaac cttcagacta ctttcctctg ctttcagcaa ggggcgttgc ccacattctc 300
tgagggctcag tggaagaacc tagactccca ttgctagagg tagaaagggg aagggtgctg 360
gggag

```

&lt;210&gt; 390

&lt;211&gt; 221

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(221)

&lt;223&gt; n = A, T, C or G

&lt;400&gt; 390

```

tgccctctcca tcttgcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacggnnt ctcattgggtg tggaacatct ctgcttgccg ttccaggaag gcctctggct 120
gctctangag tctgancnga ntctgtgccc cantntgaca naaggaaagg cggagcttat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a 221

```

&lt;210&gt; 391

&lt;211&gt; 325

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(325)  
 <223> n = A,T,C or G

<400> 391  
 tggagcaggt cccgaggcct ccctagagcc tggggccgac tctgtgnega tgcangcttt 60  
 ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120  
 tagccagggc actgctgcc aacagccagtc cnaataccat catgtnaccc ggtgngctct 180  
 naantngat ntccanagcc ctacccatcn tagttctgct ctcccaccgg ntaccagccc 240  
 cactgcccag gaatcctaca gccagtaccc tgtcccagcg tctctaccta ccagtacgat 300  
 gagacctccg gctactacta tgacc 325

<210> 392  
 <211> 277  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(277)  
 <223> n = A,T,C or G

<400> 392  
 atattgttta actccttccct ttatatcttt taacattttc atggngaaaag gttcacatct 60  
 agtctcactt nggcnagnn ctcctacttg agtctcttcc cgggcctggn ccagtnagnaa 120  
 antaccanga accgncatgn cttanaaach ncctgggttn tgggttnntc aatgactgca 180  
 tgcagtgcac caccctgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240  
 ctgaggatac agcgcgcgct cctgtgttgc tggggaa 277

<210> 393  
 <211> 566  
 <212> DNA  
 <213> Homo sapiens

<400> 393  
 actagtccag tgtggtggaa ttccgcggccg cgtcgacgga caggtcagct gtctggctca 60  
 gtgatctaca ttctgaagtt gtctgaaaat gtcttcata ttaaattcag cctaaacggt 120  
 ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180  
 gagaaggtct agtttgtcca tcagcattat catgatata ggactgggta cttgggtaag 240  
 gaggggtcta ggagatctgt cccttttaga gacaccttac ttataatgaa gtatttggga 300  
 ggggtggttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360  
 catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420  
 ttctgcctca atgtttactg tgcctttgtt tttgctagtt tgtgttgttg aaaaaaaaaa 480  
 cattctctgc ctgagtttta atttttgtcc aaagttattt taatctatac aattaaaagc 540  
 ttttgcctat caaaaaaaaaa aaaaaa 566

<210> 394  
 <211> 384  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(384)  
 <223> n = A,T,C or G

&lt;400&gt; 394

```
gaacatacat gtcccggcac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60
tgcaaattng gaccggggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
gcaggaggac cgggctttta ggagttttta gctgagtgtc actgtagacc ccaaatacca 180
tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240
gaacatccag tttcctgata aggacgatgg gaaccagccc caggaccaa ttaccattac 300
agggtagcaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
tgagcagatg gtttctgagg acgt 384
```

&lt;210&gt; 395

&lt;211&gt; 399

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 395

```
ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgc 60
tctgaccttg gactccaaga cctacatcaa cagcctggct atattagatg atgagccagt 120
tatcagaggt ttcatcattg cggaaattgt ggagtctaag gaaatcatgg cctctgaagt 180
attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300
caagttctct ttggaaagcc tgggcatctc ctactacag acctctgacc atgggacggg 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac 399
```

&lt;210&gt; 396

&lt;211&gt; 403

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(403)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 396

```
tggagttntc agtgcaaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtggag gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt 403
```

&lt;210&gt; 397

&lt;211&gt; 100

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(100)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 397

```
actagtnacg tgtgggtggaa ttgcgggccg cgtcgaccta naanccatct ctatagcaaa 60
tccatccccg ctctgggttg gtnacagaat gactgacaaa 100
```

&lt;210&gt; 398

&lt;211&gt; 278



<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(278)  
<223> n = A,T,C or G

<400> 398  
gcggccgcgt cgacagcagt tccgccagcg ctcccccctg ggtggggatg tgctgcacgc 60  
ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120  
tcaactactgt gcctcgacca gtgaggagag ctggaccgac agcgagggtg actcatcatg 180  
ctccggggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240  
ctatggccgc ttcattangt ggctcaacaa ggagaagg 278

<210> 399  
<211> 298  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(298)  
<223> n = A,T,C or G

<400> 399  
acggagggtg aggaagcgnc cctgggatcg anaggatggg tectgncatt gaccncctcn 60  
gggggtgccng catggagcgc atgggcgcgg gcctggggcca cggcatggat cgcgtgggct 120  
ccgagatcga gcgcatgggc ctggtcatgg accgcatggg ctccgtggag cgcgtgggct 180  
ccggcattga gcgcatgggc ccgctgggccc tgcaccacat ggcctccanc attganccga 240  
tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcattggg 298

<210> 400  
<211> 548  
<212> DNA  
<213> Homo sapiens

<400> 400  
acatcaacta cttcctcatt ttaaggatat gcagttccct tcateccctt ttcctgcctt 60  
gtacatgtac atgtatgaaa tttccttctc ttaccgaact ctctccacac atcacaagg 120  
caaagaacca cagcttaga agggtaagag ggcaccctat gaaatgaaat ggtgatttct 180  
tgagtctctt tttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240  
tgcagagggc tagagaatta tttcatacag gctttgaggc caccatgtc acttatcccg 300  
tataccctct caccatcccc ttgtctactc tgatgcccc aagatgcaac tgggcagcta 360  
gttggcccca taattctggg cttttgttgt ttgttttaat tacttgggca tcccaggaag 420  
ctttccagtg atctctacc atgggcccc ctcctgggat caagccctc ccaggccctg 480  
tccccagccc ctctgcccc agcccacccg cttgccttgg tgctcagccc tccattggg 540  
agcaggtt 548

<210> 401  
<211> 355  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(355)  
<223> n = A,T,C or G

<400> 401  
actgtttcca tggtatgttt ctacacattg ctacctcagt gctcctggaa acttagcttt 60  
tgatgtctcc aagtagtcca ccttcattta actctttgaa actgtatcat ctttgccaag 120  
taagagtggg ggctattttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180  
tataaatgaa tgtgctgaag caaagtggcc atgggtggcg cgaagaagan aaagatgtgt 240  
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300  
cccttttgca ttgccaagtg ccataacctat gagcactact ctaccatggn tctgc 355

<210> 402  
<211> 407  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(407)  
<223> n = A,T,C or G

<400> 402  
atggggcaag ctggataaag aaccaagacc cactggagta tggtgtcttc aagaaaccca 60  
tctcacatgc ggtggcatac ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120  
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180  
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240  
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300  
ttgtggagct tctcccctgc agagagtcct tgatctccca aaatttggtt gagatgtaag 360  
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa 407

<210> 403  
<211> 303  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(303)  
<223> n = A,T,C or G

<400> 403  
cagtatttat agccnaactg aaaagctagt agcaggcaag tctcaaatcc aggcaccaa 60  
tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120  
tagagaacaa gacctactca gtcataaaca aaaaggcaga caccaacatg gatctcatgg 180  
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240  
tcttaacaac gaccgaaacc cattatttac ataaacctcc attcggtaac catgttgaaa 300  
gga 303

<210> 404  
<211> 225  
<212> DNA  
<213> Homo sapiens

<400> 404  
aagtgtact tttaaaaatt tagtggattt tgaaaattct tagaggaaag taaaggaaaa 60  
attgttaatg cactcattta cctttacatg gtgaaagttc tctcttgatc ctacaaacag 120  
acattttcca ctctgttttc catagtgttt aagtgtatca gatgtgttgg gcatgtgaat 180  
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat 225

<210> 405

<211> 334  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(334)  
 <223> n = A,T,C or G

<400> 405  
 gagctgttat actgtgagtt ctactaggaa atcatcaaat ctgaggggttg tctggaggac 60  
 ttcaatacac ctccccccat agtgaatcag cttccagggg gtccagtcct tctccttact 120  
 tcatcccatat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctaggc 180  
 ttcccagtgct ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240  
 ctggtgagggt tgtgcctcga gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300  
 cactctccac tctctcanng tggatccac, ccct 334

<210> 406  
 <211> 216  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(216)  
 <223> n = A,T,C or G

<400> 406  
 tttcatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60  
 gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120  
 acnaaacaca aattttnatgt tgcacccttg tttctacacc tgtgggttat gacaaagaca 180  
 actgccaaag aatnttcaag aaggaggact gccant 216

<210> 407  
 <211> 413  
 <212> DNA  
 <213> Homo sapiens

<400> 407  
 gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60  
 gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120  
 gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180  
 cccagaggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240  
 ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300  
 tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360  
 tgggagttcc agaaaaagtt aaaacagaca atgggcccagg ttctgtagta aag 413

<210> 408  
 <211> 183  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(183)  
 <223> n = A,T,C or G

<400> 408

```

ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tnccttaacta gttaatcctt aaagggtctan ntaatcctta actagtcctt ccattgtgag 120
cattatcctt ccagtattcn ccttctnttt tattttactcc ttcctggcta cccatgtact 180
ntt 183

```

<210> 409

<211> 250

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(250)

<223> n = A,T,C or G

<400> 409

```

cccacgcatg ataagctctt tattttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180
gcttcccagt gcccccagga cagcgtgggc tatgtttaca ggcgttctt gctggggggg 240
ggccttatgc 250

```

<210> 410

<211> 306

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(306)

<223> n = A,T,C or G

<400> 410

```

ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtcttgcaa tccatttgc aggatccgtc tgtgcacatg cctctgtaga gaggcagatt 120
cccagggacc ttggaaacag ttggcactgt aaagtgcttg ctcccaga cacaacctaa 180
aaggtgttgt aatgggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240
nactggttgg ctttttttgn atctttttta aactggaaag ttcaattgng aaaatgaata 300
tentgc 306

```

<210> 411

<211> 261

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(261)

<223> n = A,T,C or G

<400> 411

```

agagatattn cttaggtnaa agttcataga gtcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggngaggcaa a 261

```

<210> 412

<211> 241  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(241)  
 <223> n = A,T,C or G

<400> 412  
 gttcaatggt acctgacatt tctacaacac ccactcacc gatgtattcg ttgccagtg 60  
 ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgccagg aaatactacg 120  
 actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180  
 ctgggagatt tcaactggga cattgaattc ccaaactacc cangcaatta cccagccaac 240  
 a 241

<210> 413  
 <211> 231  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(231)  
 <223> n = A,T,C or G

<400> 413  
 aactcttaca atccaagtga ctcatctgtg tgcttgaatc cttccactg tctcatctcc 60  
 ctcatccaag tttctagtag cttctctttg ttgtgaagga taatcaaaact gaacaacaaa 120  
 aagtttactc tcctcatttg gaacctaaaa actctcttct tcctgggtct gagggtctca 180  
 agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t 231

<210> 414  
 <211> 234  
 <212> DNA  
 <213> Homo sapiens

<400> 414  
 actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60  
 gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct agagaaggct 120  
 gtgagccaag gagggagggt cttccttttg catgggatgg ggatgaagta aggagaggga 180  
 ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca 234

<210> 415  
 <211> 217  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(217)  
 <223> n = A,T,C or G

<400> 415  
 gcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60  
 caaaacacag accaggtagc aaatctccac tgctctaagg ntctcaccac cactttctca 120  
 cacctagcaa tagtagaatt cagtctact tctgaggcca gaagaatggt tcagaaaaat 180  
 antggattat aaaaaataac aattaagaaa aataatc 217

<210> 416  
 <211> 213  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(213)  
 <223> n = A,T,C or G

<400> 416  
 atgcataatnt aaagganact gcctcgcttt tagaagacat ctgggctgct ctctgcatga 60  
 ggcacagcag taaagctctt tgattcccag aatcaagaac tctccccttc agactattac 120  
 cgaatgcag gtgggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180  
 atattggaac agatggagtc tctactacaa aag 213

<210> 417  
 <211> 303  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(303)  
 <223> n = A,T,C or G

<400> 417  
 nagtcttcag gcccatcagg gaagttcaca ctggagagaa gtcatacata tgtactgtat 60  
 gtgggaaagg ctttactctg agttcaaata ttcaagccca tcagagagtc cacactggag 120  
 agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180  
 ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240  
 tcantcaaag ttctgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300  
 agt 303

<210> 418  
 <211> 328  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(328)  
 <223> n = A,T,C or G

<400> 418  
 tttttggcgg tgggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60  
 tgcacaggca tgatctcggc tcaactacaac ccctgcctcc catgtccaag cgattcttgt 120  
 gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacacca gctagttttt 180  
 gtatttttag tagagacagg gtttcacat gttggccagg ctggtctcaa actcctnacc 240  
 tcagnggtca ggctggtctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300  
 aaagtgctan gattacaggc cgtgagcc 328

<210> 419  
 <211> 389  
 <212> DNA  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(389)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 419

```
cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatt 60
accctgagc catggactgg agcctgaaag gcagcgtaca ccctgctcct gatcttgctg 120
cttgtttctt ctctgtggct ccattcatag cacagttgtt gcactgaggc ttgtgcaggc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggg gtgccaggca 240
ccggttctcc agccaccaac ctcaactcgt cccgcaaatg gcacatcagt tcttctaccc 300
taaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc agccatcacg 360
tggcagccac tcnngctgtg tcgacgcgg 389
```

&lt;210&gt; 420

&lt;211&gt; 408

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 420

```
gttcctccta actcctgcc aaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtgtt tgacttttgt gtttcggcat ggagaccgaa 180
gtcccattga cacctttcc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gattcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg aagtgcctat acaaacctgg caagcccg 408
```

&lt;210&gt; 421

&lt;211&gt; 352

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(352)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 421

```
gctcaaaaat ctttttactg atnngcatgg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggctt tttttgggtc cttcttctcc accacnata acttgcatgc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacagggt tagaaacaag 240
ggtgcaacat gaaatttctg tttcgtagca agtgcattgc tcacaagttg gcangtctgc 300
cactccgagt ttattgggtg tttgtttcct ttgagatcca tgcatttctt gg 352
```

&lt;210&gt; 422

&lt;211&gt; 337

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 422

```
atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gcgatagcaa ggtgcggcgg atcgcggcgg cgtcaatcct ggccaaggtc agccgtgatc 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggtc 240
atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccg attcacccag 300
gcttcttcgg ccggtacggc tggcctatga aaattat 337
```

<210> 423  
 <211> 310  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(310)  
 <223> n = A,T,C or G

<400> 423  
 gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60  
 aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120  
 tcactgaeag aacagggtctt ttttgggtcc ttcttctcca ccacgatata cttgcagtcc 180  
 tccttcttga agattctttg gcagttgtct ttgtcataac ccacagggtgt anaaacaagg 240  
 gtgcaacatg aaatttctgt ttctagcaaa gtgcatgtct cacagttgtc aagtctgccc 300  
 tccgagttta 310

<210> 424  
 <211> 370  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(370)  
 <223> n = A,T,C or G

<400> 424  
 gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60  
 ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120  
 cactgacaga acagggtottt ttttgggtcct tcttctccac cacgatatac ttgcagtcc 180  
 ccttcttgaa gattcttttg cagttgtctt tgtcataacc cacagggtga gaaacatcct 240  
 ggttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300  
 cacgaagggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360  
 tccgtcgacg 370

<210> 425  
 <211> 216  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(216)  
 <223> n = A,T,C or G

<400> 425  
 aattgctatn ntttattttg ccaactcaaaa taattaccaa aaaaaaaaaa tnttaaatga 60  
 taacaacnca acatcaaggn aananaaca ggaatgntg actntgcata aatnggccga 120  
 anattatcca ttatnttaag ggttgacttc aggntacagc acacagacaa acatgcccag 180  
 gagntntca ggaccgctcg atgtntntg aggagg 216

<210> 426  
 <211> 596  
 <212> DNA  
 <213> Homo sapiens



```

<400> 426
cttccagtga ggataaccct gttgccccgg gccgagggtc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gcccgaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggcc ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctggctgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
ggtggatggc cttttcagct ttaaccaat ttgactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtcccgtgg tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct 596

```

```

<210> 427
<211> 107
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(107)
<223> n = A,T,C or G

```

```

<400> 427
gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagn 107

```

```

<210> 428
<211> 38
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(38)
<223> n = A,T,C or G

```

```

<400> 428
gaacttcna anaangactt tattcactat ttacatt 38

```

```

<210> 429
<211> 544
<212> DNA
<213> Homo sapiens

```

```

<400> 429
ctttgctgga cggaataaaa gtggacgcaa gcatgaccto ctgatgaggg cgctgcattt 60
attgaagagc ggctgcagcc ctgcggttca gattaaaatc cgagaattgt atagacgccg 120
atatccacga actcttgaag gactttctga tttatccaca atcaaatcat cggttttcag 180
tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
gccttccact tcagttacac ctactcacc atcctctcct gttggttctg tgctgcttca 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggtattt ttgccagggtg gtaggagaga 540
ttat 544

```

```

<210> 430

```

<211> 507  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(507)  
 <223> n = A,T,C or G

<400> 430  
 cttatcncaa tggggctccc aaacttggct gtgcagtggg aactccgggg gaattttgaa 60  
 gaacactgac acccatcttc caccgccgaca ctctgattta attgggctgc agtgagaaca 120  
 gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180  
 ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240  
 attcaactag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300  
 caagaaggag gactgcaagt atatcgtggg ggagaagaag gacccaaaaa agacctgttc 360  
 tgtcagtga tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420  
 cattctctc tggcctctaa tagtcaatga ttgtgtagcc atgcctatca gtaaaaagat 480  
 ttttgagcaa aaaaaaaaaa aaaaaaa 507

<210> 431  
 <211> 392  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(392)  
 <223> n = A,T,C or G

<400> 431  
 gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60  
 aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120  
 tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180  
 aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240  
 catcattcca gcattctgag attaggngga ttggggatca ttctggagtt ggaatgttca 300  
 acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaagg 360  
 gcaatgagtc tggctttttac tctgtgtgtt ct 392

<210> 432  
 <211> 387  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(387)  
 <223> n = A,T,C or G

<400> 432  
 ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60  
 aaatgcaagg caacatgtgt agatctcttt tcttattctt ttgtctataa tactgtattg 120  
 ngtagtccaa gtcctcggn a gtcagccac tngaaacat gtcctcttta gattaacctc 180  
 gtggacnctn tgttgnatt gtctgaactg tagngccctg tattttgctt ctgtctgnga 240  
 attctgttgc ttctggggca ttctcttng atgcagagga ccaccacaca gatgacagca 300  
 atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360  
 acaacgtata gaacactgga gtccttt 387

<210> 433  
 <211> 281  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(281)  
 <223> n = A,T,C or G

<400> 433  
 ttcaactagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60  
 ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120  
 caggcnctat ttgggttggc tggaggagct gtggaaaaca tggagagatt ggcgctggag 180  
 atcgccgtgg ctattcctcn ttgntattac accagngagg ntctctgtnt gccactgggt 240  
 tnnaaaaccg ntatacaata atgatagaat aggacacaca t 281

<210> 434  
 <211> 484  
 <212> DNA  
 <213> Homo sapiens

<400> 434  
 ttttaaaata agcatttagt gctcagtcct tactgagtag tctttctctc cctcctctg 60  
 aatttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120  
 tgttgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180  
 tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240  
 agctagtcta tcagcatctg acagggtgaat tggatggttc tcagaaccat ttcaccaga 300  
 cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca taacaaacc 360  
 tgctccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420  
 tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag taccatgtc 480  
 tttta 484

<210> 435  
 <211> 424  
 <212> DNA  
 <213> Homo sapiens

<400> 435  
 gcgccgtca gagcaggtca ctttctgcct tccacgtcct ccttcaagga agccccatgt 60  
 gggtagcttt caatatcgca ggttcttact cctctgcctc tataagctca aaccaccaa 120  
 cgatcgggca agtaaaccac ctccctcgcc gacttcggaa ctggcgagag ttcagcgag 180  
 atgggcctgt ggggagggg caagatagat gagggggagc ggcaggtgc ggggtgacc 240  
 cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggcct 300  
 ggtagagacc tttgggggtc tggaaacctt ggactcccca tgctctaact cccacactct 360  
 gctatcagaa acttaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420  
 aaac 424

<210> 436  
 <211> 667  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_f ature  
 <222> (1)...(667)  
 <223> n = A,T,C or G

&lt;400&gt; 436

```

accttgggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tcctggccat gtaatcctga aagttttccc aaggtagcta taaaatcctt ataagggtgc 120
agcctcttct ggaattcctc tgatttcaaa gtctcactct caagttcttg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacaggggt 300
gccaggtttg tcatagcact catcaaagtc cggtcacagt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctatata tctttcttat atactctcca 420
agttcataat gctgctccat gccagctgg gtgagttggc caaatccttg tggccatgag 480
gattccttta tggggtcagt gggaaagggt tcaatgggac ttcggctccc atgccgaac 540
accaaagtca caaacttcaa ctccctgggt agtacacttc ggtctagcca gaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tgttgag 667

```

&lt;210&gt; 437

&lt;211&gt; 693

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 437

```

ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacagccag gtaaggaaag ctggattggc acactaggac tctaccatac cgggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaaact tcagacagct ttttcagatc 180
ataaaagata attcttagcc catgtttctt tccagagcag acctgaaatg acagcacagc 240
aggtactcct ctatttttcac cctcttggt tctactctct ggcagtcaga cctgtgggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
catttctcca ggttacccta ggtgtcacta ttgggggggac agccagcatc tttagctttc 420
atttgatttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tcctatttct aggcactgag ggctgtgggg taccttgtgg tgccaaaaca gatcctgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc 693

```

&lt;210&gt; 438

&lt;211&gt; 360

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 438

```

ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgaggagg ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcc aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360

```

&lt;210&gt; 439

&lt;211&gt; 431

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(431)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 439

```

gttcctnnta actcctgcc aagacagctc tcctcaacat gagagctgca cccctcctcc 60

```

```

tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgg gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcattggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtccctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t                                     431

```

&lt;210&gt; 440

&lt;211&gt; 523

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 440

```

agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaaggga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaagtgc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaaattaa aacctctttg tgtcccttgg tcttggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaac acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcacttga tgagaacaag cta                                     523

```

&lt;210&gt; 441

&lt;211&gt; 430

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 441

```

gttcctccta actcctgcca gaaacagctc tcttcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgg gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcattggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtccctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag                                     430

```

&lt;210&gt; 442

&lt;211&gt; 362

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 442

```

ctaaggaatt agtagtggtc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcttgga tgacaattat attttaactt tgggtgggga aagagttata ggaccacagt 120
cttcacttct gatacttgta aattaactct ttattgcact tgttttgacc attaagctat 180
atgttttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatatt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
tc                                     362

```

&lt;210&gt; 443

&lt;211&gt; 624

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(624)  
 <223> n = A,T,C or G

<400> 443  
 tttttttttt gcaacacaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60  
 ttgaaagaat taaattcaga ggaggggaga gaaagagtag tcagtaggga ctgagcacta 120  
 aatgcttatt ttaaaagaaa tgtaaagagc agaaagcaat tcaggctacc ctgccttttg 180  
 tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacattg caatgtggag 240  
 cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaaccttg cttcctgttt 300  
 tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc ttaaatgaac 360  
 taacgcctac aaaacactta aacatagata acatagggtgc aagtactatg tatctgggtac 420  
 atggtaaaca tccttattat taaagtcaac gctaaaatga atgtgtgtgc atatgctaata 480  
 agtacagaga gagggcactt aaaccaacta agggcctgga ggggaagggtt cctggaaaga 540  
 ngatgcttgt gctgggtcca aatcttgggtc tactatgacc ttggccaaat tatttaaact 600  
 ttgtccctat ctgctaataa gatc 624

<210> 444  
 <211> 425  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(425)  
 <223> n = A,T,C or G

<400> 444  
 gcacatcatt nntcttgcatt tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60  
 gaagctttgt ccaggcctgt gtgtgaaccc aatgttttgc ttagaaatag aacaagtaag 120  
 ttcattgcta tagcataaca caaaatttgc ataagtgggtg gtcagcaaat ccttgaatgc 180  
 tgcttaatgt gagagggttg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240  
 gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300  
 cctctgcaat ctgccacctc ctgctggcag gatttgtttt tgcctcctgt gaagagccaa 360  
 ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420  
 gtaga 425

<210> 445  
 <211> 414  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(414)  
 <223> n = A,T,C or G

<400> 445  
 catgtttatg nttttggatt actttgggca cctagtgttt ctaaatcgtc tatcattctt 60  
 ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatctt caagtctttg 120  
 tgaaattctt tgcatgtggc agattatttg atgtagtttc ctttaactag catataaatc 180  
 tgggtgtgtt cagataaatg aacagcaaaa tgtgggtggaa ttaccatttg gaacattgtg 240  
 aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300  
 ggatttttat aatcctactc acaaatgact aggtctctcc tcttgtattt tgaagcagtg 360  
 tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcgaattta gtag 414

<210> 446

<211> 631  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(631)  
<223> n = A,T,C or G

<400> 446  
acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60  
tctgcatgca tgggaagtgt gagcattcta tcaatatgca ggagccatct tgcagggtgtg 120  
atgctgggta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttggtc 180  
ccggtcctgt acgatttcag tatgtcttaa tcgcagctgt gattggaaca attcagattg 240  
ctgtcactgt tgtgggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300  
actgagattt gtaaactttc caaccttcca ggaaatgcc cagaagcaac agaattcaca 360  
gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgagggt 420  
taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttggc ctacacaata 480  
cagtattata gacaaaagaa taagacaaga gatctacaca tgttgcttgg catttggtgtg 540  
aatctacacc aatgaaaaca tgtactacag ctatatattga ttatgtatgg atatatttga 600  
aatagtatac attgtcttga tgttttttct g 631

<210> 447  
<211> 585  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(585)  
<223> n = A,T,C or G

<400> 447  
ccttgggaaa antntcacia tataaagggt cgtagacttt actccaaatt ccaaaaagggt 60  
cctggccatg taatcctgaa agttttccca aggtagctat aaaatcctta taagggtgca 120  
gcctcttctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180  
agttcctgaa aggcaggtat agcaactgat cttcagaaag aggaactgtg tgcaccggga 240  
tgggctgcca gagtaggata ggattccaga tgctgacacc ttctggggga aacagggctg 300  
ccaggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360  
gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420  
gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480  
attcctttat ggggtcagtg ggaaagggtg caatgggact tcggtctcca tgccgaaaca 540  
ccaaagtcac aaacttcaac tccttggcta gtacacttcg gtcta 585

<210> 448  
<211> 93  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(93)  
<223> n = A,T,C or G

<400> 448  
tgctcgtggg tcattctgan ncccgaactg accntgcccag ccctgcccgan gggccnccat 60  
ggctccctag tgccctggag agganggggc tag 93

<210> 449  
 <211> 706  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(706)  
 <223> n = A,T,C or G

<400> 449  
 ccaagttcat gctntgtgct ggacgctgga cagggggcga aagcnnttgc tcgtgggtca 60  
 ttctganac cgaactgacc atgccagccc tgccgatggt cctccatggc tccctagtgc 120  
 cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180  
 cggggacagc atcctgcaga tggtcgggcg cgtcccattc gccattcagg ctgcgcaact 240  
 gttgggaagg gcgatcggtg cgggcctctt cgctattacg ccagctggcg aaagggggat 300  
 gtgctgcaag gcgattaagt tgggtaacgc caggggtttc ccagtncga cgttgtaaaa 360  
 cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcattgcacg 420  
 cgtacgtaag cttggatcct ctagagcgcg cgcctactac tactaaattc gcggccgcgt 480  
 cgacgtggga tccnactga gagagtggag agtgacatgt gctggacnct gtccatgaag 540  
 cactgagcag aagctggagg cacaacgcnc cagacactca cagctactca ggaggctgag 600  
 aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncccca 660  
 gcatggatga cagagtgaaa ctccatctta aaaaaaaaaa aaaaaa 706

<210> 450  
 <211> 493  
 <212> DNA  
 <213> Homo sapiens

<400> 450  
 gagacggagt gtcactctgt tgcccagggt ggagtgcagc aagacactgt ctaagaaaaa 60  
 acagttttaa aaggtaaaac aacataaaaa gaaatatcct atagtggaaa taagagagtc 120  
 aaatgaggct gagaacttta caaagggatc ttacagacat gtccgccaata tcaactgcatg 180  
 agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240  
 caagtcaggt agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300  
 agagacactg tcagagagtt aaaaagttag ttctatccat gaggtgattc cacagtcttc 360  
 tcaagtcAAC acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420  
 tacacatcag aatcacctgg agagctttac aaactcccat tgccgagggt cgacgcggcc 480  
 gcgaatttag tag 493

<210> 451  
 <211> 501  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(501)  
 <223> n = A,T,C or G

<400> 451  
 gggcgcgtcc cattcgccat tcaggctgcg caactgttgg gaagggcgat cgggtcgggc 60  
 ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120  
 aacgccaggg ttttccagc cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180  
 tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240  
 gcggccgcct actactacta aattcgcggc cgcgtcgacg tgggatccnc actgagagag 300  
 tggagagtga catgtgctgg acnctgtcca tgaagcactg agcagaagct ggaggcacia 360  
 cgcncacagac actcacagct actcaggagg ctgagaacag gttgaacctg ggagggtggag 420



gttgcaatga gctgagatca ggccnctgcn ccccgatg gatgacagag tgaactcca 480  
tcttaaaaaa aaaaaaaaaa a 501

<210> 452  
<211> 51  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(51)  
<223> n = A,T,C or G

<400> 452  
agacgggttc accnttataa cnccttttag gatgggnntt ggggagcaag c 51

<210> 453  
<211> 317  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(317)  
<223> n = A,T,C or G

<400> 453  
tacctcttgc tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa 60  
acatctgaag agctagtcta tcagcatctg gcaagtgaat tggatgggtc tcagaacccat 120  
ttcaccana cagcctgttt ctatcctgtt taataaatta gtttgggtc totacatgca 180  
taacaaaccc tgtccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240  
cccacaaac tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300  
tacctatgct tttatta 317

<210> 454  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 454  
ttcgaggtac aatcaactct cagagtgtag tttccttcta tagatgagtc agcattaata 60  
taagccacgc cagctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120  
agaagaccaa attcttctgc atcccagctt gcaaacaaaa ttgttcttct aggtctccac 180  
ccttcctttt tcagtgttcc aaagctcctc acaatttcat gaacaacagc t 231

<210> 455  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 455  
taccaaagag ggcataataa tcagtctcac agtaggggtc accatcctcc aagtgaaaaa 60  
cattgttccg aatgggcttt ccacaggcta cacacacaaa acaggaaaca tgccaagttt 120  
gtttcaacgc attgatgact totccaagga tcttcctttg gcatcgacca cattcagggg 180  
caaagaattt ctcatagcac agtcacaaat acagggtctc tttctcctct a 231

<210> 456  
<211> 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 456

```

ttggcaggta cccttacaaa gaagacacca taccttatgc gttattaggt ggaataatca 60
ttccattcag tattatcggt attattcttg gagaaacct gtctgtttac tgtaaccttt 120
tgcactcaaa ttccctttatc aggaataact acatagccac tatttacaaa gccattggaa 180
cctttttatt tgggtgcagct gctagtcagt ccctgactga cattgccaag t 231

```

&lt;210&gt; 457

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt; \*

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(231)

&lt;223&gt; n = A, T, C or G

&lt;400&gt; 457

```

cgaggtagcc aggggtctga aaatctctnn tttantagtc gatagcaaaa ttgttcatca 60
gcattcctta atatgatctt gctataatta gatttttctc cattagagtt catacagttt 120
tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g 231

```

&lt;210&gt; 458

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 458

```

agggtctggt cccccactt ccactcccct ctactctctc taggactggg ctgggccaag 60
agaagagggg tgggttaggg agccgttgag acctgaagcc ccaccotcta ccttccttca 120
acaccctaac cttgggtaac agcatttgga attatcattt gggatgagta gaatttccaa 180
ggtcctgggt taggcatttt ggggggccag accccaggag aagaagattc t 231

```

&lt;210&gt; 459

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 459

```

ggtaccgagg ctgctgaca cagagaaacc ccaacgcgag gaaaggaatg gccagccaca 60
ccttcgcaaa acctgtggtg gcccaccagt cctaacggga caggacagag agacagagca 120
gccctgcact gttttccctc caccacagcc atcctgtccc tcattggctc tgtgctttcc 180
actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a 231

```

&lt;210&gt; 460

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 460

```

gcagggtata catgctgcaa caacagatgt gactaggaac ggccggtgac atggggaggg 60
cctatcaccc tattcttggg ggctgcttct tcacagtgat catgaagcct agcagcaaat 120
cccacctccc cacacgcaca cggccagcct ggagcccaca gaagggtcct cctgcagcca 180
gtggagcttg gtccagcctc cagtccaccc ctaccaggct taaggataga a 231

```

&lt;210&gt; 461

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 461

cgagggtttga gaagctctaa tgtgcagggg agccgagaag caggcggcct agggaggggtc 60  
gcgtgtgctc cagaagagtg tgtgcatgcc agaggggaaa caggcgctg tgtgtcctgg 120  
gtggggttca gtgaggagtg ggaaattggg tcagcagaac caagccgttg ggtgaataag 180  
agggggattc catggcactg atagagccct atagtttcag agctgggaat t 231

&lt;210&gt; 462

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 462

aggtaccctc attgtagcca tgggaaaatt gatgttcagt ggggatcagt gaattaaatg 60  
gggtcatgca agtataaaaa ttaaaaaaaa aagacttcat gcccaatctc atatgatgtg 120  
gaagaactgt tagagagacc aacagggtag tgggttagag atttccagag tcttacattt 180  
tctagaggag gtatttaatt tcttctcact catccagtgt tgtatttagg a 231

&lt;210&gt; 463

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 463

tactccagcc tgggtgacaga gcgagaccct atcaccgccc cccacccccc caaaaaaaaaa 60  
actgagtaga cagggtgtcct cttggcatgg taagtcttaa gtcccctccc agatctgtga 120  
catttgacag gtgtcttttc ctctggacct cggtgtcccc atctgagtga gaaaaggcag 180  
tggggagggtg gatcttccag tcgaagcggg atagaagccc gtgtgaaaag c 231

&lt;210&gt; 464

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 464

gtactctaa agttttatcta agttgccttt tctgggtggg aaagtttaac cttagtgtgact 60  
aaggacatca catatgaaga atgtttaagt tggaggtggc aacgtgaatt gcaaacaggg 120  
cctgtctcag tgactgtgtg cctgtagtcc cagctactcg ggagtctgtg tgaggccagg 180  
ggtgccagcg caccagctag atgctctgta acttctaggg cccattttcc c 231

&lt;210&gt; 465

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 465

catgttggtg tagctgtggt aatgctggct gcattctcaga cagggttaac ttcagctcct 60  
gtggcaaatt agcaacaaat tctgacatca tatttatggt ttctgtatct ttgttgatga 120  
aggatggcac aatttttgct tgtgttcata atatactcag attagttcag ctccatcaga 180  
taaactggag acatgcagga cattagggtg gtgtttagc tctggtaatg a 231

&lt;210&gt; 466

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 466

caggtacctc	tttccattgg	atactgtgct	agcaagcatg	ctctccgggg	tttttttaat	60
ggccttcgaa	cagaacttgc	cacataccca	ggtataatag	tttctaacat	ttgcccagga	120
cctgtgcaat	caaataattgt	ggagaattcc	ctagctggag	aagtcacaaa	gactataggg	180
aataatggag	accagtccca	caagatgaca	accagtcgtt	gtgtgcggct	g	231

&lt;210&gt; 467

&lt;211&gt; 311

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 467

gtacaccttg	gcacagtcca	atctgaactg	gttcggcact	catctttcat	gagatggatg	60
tgggtggcttt	tctccttttt	catcaagact	cctcagcagg	gagcccagac	cagcctgcac	120
tgtgccttaa	cagaaggctc	tgagattcta	agtgggaatc	atttcagtga	ctgtcatgtg	180
gcatgggtct	ctgcccaagc	tcgtaatgag	actatagcaa	ggcggctgtg	ggacgtcagt	240
tgtgacctgc	tgggcctccc	aatagactaa	caggcagtgc	cagttggacc	caagagaaga	300
ctgcagcaga	c					311

&lt;210&gt; 468

&lt;211&gt; 3112

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 468

cattgtgttg	ggagaaaaac	agagggggaga	tttgtgtggc	tgagccgag	ggagaccagg	60
aagatctgca	tgggtgggaag	gacctgatga	tacagagttt	gataggagac	aattaaaggc	120
tggaaggcac	tggatgcctg	atgatgaagt	ggactttcaa	actggggcac	tactgaaacg	180
atgggatggc	cagagacaca	ggagatgagt	tggagcaagc	tcaataacaa	agtgggtcaa	240
cgaggacttg	gaattgcatg	gagctggagc	tgaagttag	cccaattggt	tactagttag	300
gtgaatgtgg	atgattggat	gatcatttct	catctctgag	cctcagggtc	cccatccata	360
aaatgggata	cacagtatga	tctataaagt	gggatatagt	atgatctact	tcactgggtt	420
atttgaagga	tgaattgaga	taattttatt	caggtgccta	gaacaatgcc	cagattagta	480
catttgggtg	aactgagaaa	tggcataaca	ccaaatttaa	tatatgtcag	atgttactat	540
gattatcatt	caatctcata	gttttgtcat	ggcccaattt	atcctcactt	gtgcctcaac	600
aaattgaact	gttaacaaag	gaatctctgg	tcctgggtaa	tggctgagca	ccactgagca	660
tttccattcc	agttggcttc	ttgggtttgc	tagctgcac	actagtcac	ttaaataaat	720
gaagttttta	catttctcca	gtgatttttt	tatctcacct	ttgaagatac	tatgttatgt	780
gattaaataa	agaacttgag	aagaacaggt	ttcattaaac	ataaaatcaa	tgtagacgca	840
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&lt;210&gt; 469

&lt;211&gt; 2229

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 469

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&lt;211&gt; 2426

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 490

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aaaaaaaaa

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&lt;210&gt; 474

&lt;211&gt; 1594

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 474

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&lt;210&gt; 475

&lt;211&gt; 2414

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; (33)

&lt;223&gt; n=A, T, C or G

&lt;400&gt; 475

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<211> 3434  
<212> DNA  
<213> Homo sapiens

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<210> 477
<211> 140
<212> PRT
<213> Homo sapiens
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<400> 477																
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				5					10						15	
His	Tyr	His	Arg	Asp	Thr	Asp	Thr	Arg	Arg	His	His	His	Met	Asp	Thr	
			20					25					30			
Leu	Ser	His	Tyr	His	Arg	Asp	Thr	Arg	His	His	Thr	Val	Thr	Trp	Thr	
		35					40					45				
His	His	His	Thr	His	Glu	His	Thr	Asp	Thr	Leu	Pro	Tyr	Gly	His	Trp	
	50					55					60					
His	Thr	His	Cys	His	Thr	Val	Thr	Trp	Thr	His	Leu	His	Thr	Ile	Thr	
65					70					75					80	
Pro	Pro	His	Thr	Leu	Pro	Val	Asp	Thr	Arg	Thr	His	Arg	His	Cys	His	
				85					90					95		
Thr	Asp	Thr	Gln	Asn	Thr	Val	Thr	Arg	Arg	His	His	His	Ala	Asp	Thr	
			100					105					110			
Pro	Pro	Leu	Trp	Cys	Arg	Leu	Asn	Tyr	Pro	Ala	Gly	Gly	Thr	Ala	Val	
		115					120					125				
Ala	Tyr	Ser	Cys	Leu	Ser	Asp	Trp	Leu	Ser	Pro	Gln					
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<210> 478  
<211> 143  
<212> PRT  
<213> Homo sapiens
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<400> 478
Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln
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Ser His Gly His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr
                20                      25                      30

Gly Glu Ile Thr Trp Thr His His His Thr Ile Thr Gly Thr Gln Thr
        35                      40                      45

His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr

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50 55 60  
 Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr  
 65 70 75 80  
 Pro Thr His Cys His Met Asp Thr Gly Thr His Thr Ala Thr Leu Ser  
 85 90 95  
 His Gly His Thr Ser Thr Pro Ser His His His Thr His Cys Leu Trp  
 100 105 110  
 Thr Gln Gly His Thr Asp Thr Val Thr Gln Ile His Lys Thr Leu Ser  
 115 120 125  
 His Gly Asp Ile Thr Met Gln Ile His His His Ser Gly Ala Val  
 130 135 140

<210> 479  
 <211> 222  
 <212> PRT  
 <213> Homo sapiens

<400> 479  
 Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln  
 5 10 15  
 Ser His Glu His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr  
 20 25 30  
 Gly Glu Ile Thr Leu Thr His His His Thr Ile Thr Gly Thr Gln Thr  
 35 40 45  
 His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr  
 50 55 60  
 Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr  
 65 70 75 80  
 Pro Thr His Cys His Met Asp Thr Ala Thr His Thr Ala Thr Leu Ser  
 85 90 95  
 His Gly His Thr Ser Ile Pro Ser His His His Thr His Cys His Val  
 100 105 110  
 Asp Thr Arg Thr His Arg His Cys His Thr Asp Thr Gln Asn Thr Val  
 115 120 125  
 Thr Arg Arg His His His Ala Asp Thr Pro Pro His Gly His Ser Thr  
 130 135 140  
 Arg His Ser Ala Thr Gln Ile His His His Thr Glu Met Arg Thr His  
 145 150 155 160  
 Cys His Thr Asp Thr Thr Thr Ser Leu Pro His Phe His Val Ser Ala  
 165 170 175  
 Gly Gly Val Gly Pro Thr Thr Leu Gly Ser Asn Arg Glu Ile Thr Trp

180							185				190				
Thr	Tyr	Ser	Glu	Gly	Lys	Ile	Phe	Phe	Tyr	Phe	Leu	Gly	Asn	Gln	Ala
		195					200					205			
Arg	Leu	Cys	Leu	Lys	Lys	Arg	Lys	Lys	Lys	Gln	Tyr	Thr	Val		
	210					215					220				

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<210> 480
<211> 144
<212> PRT
<213> Homo sapiens
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<400> 480																	
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				5					10					15			
Cys	Cys	Leu	Trp	Gly	Leu	Gln	Ser	Leu	Pro	Gln	Gly	Ser	Tyr	Val	Thr		
			20					25					30				
Val	Gly	Phe	Leu	Val	Val	Lys	Arg	Gln	Thr	Ile	Gly	Arg	Leu	Glu	Arg		
		35					40					45					
Asp	Phe	Met	Phe	Lys	Cys	Arg	Lys	Gln	Pro	Gly	Leu	Pro	Pro	Ser	Gly		
	50					55					60						
Leu	Cys	Leu	Leu	Trp	Pro	Trp	Pro	Asn	Leu	Glu	Phe	Gly	Arg	Arg	Gln		
	65				70					75					80		
Asp	Arg	Leu	Thr	Trp	Ser	Ser	Val	Ser	Val	Ala	Gly	Val	Cys	Ala	Cys		
				85					90					95			
Arg	Ala	Arg	Pro	Gly	Trp	Leu	Gly	Glu	Gln	Pro	Ala	Thr	Ser	Ala	Gly		
			100					105					110				
Val	Arg	Leu	Glu	Gln	Val	Glu	Gln	Pro	Pro	Ala	His	Pro	Leu	Gln	Glu		
		115					120					125					
Ala	Gly	Val	Ala	Arg	Phe	Pro	Arg	Pro	Glu	Trp	Val	Pro	Pro	Asn	Gly		
	130					135					140						

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<210> 481
<211> 167
<212> PRT
<213> Homo sapiens
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<400> 481
Met His Gly Pro Gln Val Leu Ala Arg Cys Ser Glu Cys Ala Cys Pro
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Ala Leu Ala Ala Thr Ser Ala Gly Val Arg Leu Glu Gly Val Asp Arg
          20              25              30

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Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys Ser His Ser  
 35 40 45  
 Leu Ser Gly Cys His Leu Met Ala Asp Gly Ala Lys Ala Leu Gly Lys  
 50 55 60  
 Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr Asp Val Pro  
 65 70 75 80  
 Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser Ser Trp Arg  
 85 90 95  
 Ala Leu Ala Glu Val Thr Gly Cys Ser Leu Gly Pro Leu Gly Leu Ala  
 100 105 110  
 Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys Trp Ser His  
 115 120 125  
 Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr Ala Ala Phe  
 130 135 140  
 Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu Trp Ala Ser  
 145 150 155 160  
 Trp Leu Ser Arg Gly Arg Pro  
 165

<210> 482  
 <211> 143  
 <212> PRT  
 <213> Homo sapiens

<400> 482  
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 5 10 15  
 Pro Cys Leu Trp Gly Ser Ser Pro Cys Leu Arg Cys His Met Ala Leu  
 20 25 30  
 Arg Ala Ser Trp Leu Pro Gly Gly Gly Pro Gln Ala Ile Leu Gly Arg  
 35 40 45  
 Thr Leu Cys Ser Ser Ala Glu Ser Ser Gln Asp Cys His Pro Gly Gly  
 50 55 60  
 Pro Ser Ile Ala Leu Ala Lys Pro Cys Arg Gly Val Trp Leu Leu Phe  
 65 70 75 80  
 Glu Pro Ala Trp Pro Pro Trp His Ala Arg Ala Pro Gly Ala Gly Thr  
 85 90 95  
 Leu Leu Arg Val Cys Leu Ser Cys Leu Gly Cys His Leu Cys Gly Gly  
 100 105 110  
 Ala Ser Gly Gly Gly Gly Pro Ala Thr Asn Leu Thr Gln Ser Arg Lys  
 115 120 125

Trp Met Ala Met Phe Pro Gln Pro Glu Trp Leu Pro Pro Asp Gly  
 130 135 140

<210> 483  
 <211> 143  
 <212> PRT  
 <213> Homo sapiens

<400> 483  
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 Cys Cys Leu Trp Gly Ser Ser Pro Cys Leu Gly Ser Tyr Gly Thr Ala  
 20 25 30  
 Gly Phe Leu Val Ala Lys Arg Arg Thr Thr Gly Leu Leu Glu Glu Asp  
 35 40 45  
 Phe Thr Phe Lys Cys Arg Lys Gln Pro Lys Leu Pro Ser Met Arg Leu  
 50 55 60  
 Ser Leu Leu Trp Pro Trp Arg Asp Leu Lys Phe Val Pro Arg Gln Asp  
 65 70 75 80  
 Lys Leu Thr Arg Ser Ser Val Ser Val Ala Gly Ala Tyr Ala Cys Arg  
 85 90 95  
 Ala Gly Pro Gly Trp Leu Lys Glu Gln Pro Ala Thr Ser Ala Arg Val  
 100 105 110  
 Arg Leu Val Gln Ala Glu His Pro Pro Pro His Pro Leu Glu Glu Val  
 115 120 125  
 Gly Met Ala Arg Phe Pro Gln Pro Glu Cys Leu Pro Pro Tyr Cys  
 130 135 140

<210> 484  
 <211> 30  
 <212> PRT  
 <213> Homo Sapien

<400> 484  
 Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe  
 1 5 10 15  
 Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile  
 20 25 30

<210> 485  
 <211> 31  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 485  
 gggaagctta tcacctatgt gccgcctctg c



<210> 486  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 486  
 gcgaattctc acgctgagta tttggcc

27

<210> 487  
 <211> 36  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 487  
 cccgaattct tagctgcccc tccgaacgcc ttcata

36

<210> 488  
 <211> 33  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 488  
 gggaagcttc ttccccggct gcaccagctg tgc

33

<210> 489  
 <211> 19  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 489  
 Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val Tyr Leu Ala  
 1 5 10 15  
 Ser Val Ala

<210> 490  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 490  
 Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys

1 5 10 15

Leu Ser His Ser  
20

<210> 491  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 491

Thr Cys Leu Ser His Ser Val Ala Val Thr Ala Ser Ala Ala Leu  
1 5 10 15

Thr Gly Phe Thr  
20

<210> 492  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 492

Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr  
1 5 10 15

Leu Ala Ser Leu  
20

<210> 493  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 493

Tyr Thr Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro  
1 5 10 15

Lys Tyr Arg Gly  
20

<210> 494  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 494

Leu Pro Lys Tyr Arg Gly Asp Thr Gly Gly Ala Ser S r Glu Asp Ser  
1 5 10 15

Leu Met Ile Ser

20

<210> 495  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 495  
 Asp Ser Leu Met Thr Ser Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro  
 1 5 10 15  
 Phe Pro Asn Gly  
 20

<210> 496  
 <211> 21  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 496  
 Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu  
 1 5 10 15  
 Pro Pro Pro Pro Ala  
 20

<210> 497  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 497  
 Leu Leu Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val  
 1 5 10 15  
 Ser Val Arg Val  
 20

<210> 498  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 498  
 Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala Arg Val  
 1 5 10 15  
 Val Pro Gly Arg  
 20

<210> 499  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 499  
 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp  
 1 5 10 15  
 Ser Ala Phe Leu  
 20

<210> 500  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 500  
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met  
 1 5 10 15  
 Gly Ser Ile Val  
 20

<210> 501  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 501  
 Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met  
 1 5 10 15  
 Val Ser Ala Ala  
 20

<210> 502  
 <211> 414  
 <212> DNA  
 <213> Homo Sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(414)  
 <223> n=A,T,C or G

<400> 502  
 caccatggag acaggcctgc gctggctttt cctggctcgt gtgctcaaag gtgtccaatg 60  
 tcagtccgtg gaggagtccg ggggtcgcct ggtcacgcct gggacacctt tgacantcac 120  
 ctgtagagtt tttggaatng acctcagtag caatgcaatg agctgggtcc gccaggctcc 180  
 agggaagggg ctggaatgga tcggagccat tgataattgt ccacantacg cgacctgggc 240

```

gaaaggccga ttatnatntt ccaaaacctn gaccacgggtg gatttgaaaa tgaccagtcc 300
gacaaccgag gacacggcca cctatttttg tggcagaatg aatactggta atagtgggtg 360
gaagaatatt tggggcccag gcaccctggt caccgtntcc tcagggcaac ctaa 414

```

```

<210> 503
<211> 379
<212> DNA
<213> Homo Sapien

```

```

<220>
<221> misc_feature
<222> (1)...(379)
<223> n=A,T,C or G

```

```

<400> 503
atnccgatggt gcttgggtcaa aggtgtccag tgtcagtcgg tggaggagtc cggggggtcgc 60
ctggtcacgc ctgggacacc cctgacactc acctgcaccg tntctggatt ngacatcagt 120
agctatggag tgagctgggt ccgccaggct ccagggaagg ggctgggnata catcggatca 180
ttagtagtag tggtagattt tacgcgagct gggcgaaagg ccgattcacc atttccaaaa 240
cctngaccac ggtggatttg aaaatcacca gtttgacaac cgaggacacg gccacctatt 300
tntgtgccag agggggggtt aattataaag acatttgggg cccaggcacc ctggtcaccg 360
tntccttagg gcaacctaa 379

```

```

<210> 504
<211> 19
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Made in a lab

```

```

<400> 504
Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro Tyr Phe Lys Glu
1 5 10 15
Asn Ser Ala

```

```

<210> 505
<211> 20
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Made in a lab

```

```

<400> 505
Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn Asp Asn Val Thr
1 5 10 15
Asn Thr Ala Asn
20

```

```

<210> 506
<211> 407
<212> DNA
<213> Homo Sapien

```

```

<400> 506

```

```
<210> 507
<211> 422
<212> DNA
<213> Homo Sapien
```

<400> 507						
atggagacag	gcctgcgctg	gcttctcctg	gtcgcgtgtgc	tcaaagggtgt	ccagtgtcag	60
tcggtggagg	agtccggggg	tcgcctggtc	acgcctggga	caccctgac	actcacctgt	120
acagtctctg	gattctcct	cagcaactac	gacctgaact	gggtccgcca	ggctccaggg	180
aaggggctgg	aatggatcgg	gatcattaat	tatgttggt	ggacggacta	cgcgaactgg	240
gcaaaaggcc	ggttcaccat	ctccaaaacc	tcgaccaccg	tggatctcaa	gatcgccagt	300
ccgacaaccg	aggcaccggc	cacctatttc	tgtgccagag	ggtggaagtg	cgatgagtct	360
ggctcgtgct	tgcgcgcatctg	gggccaggc	accctgggtca	cgtctcctt	agggcaacct	420
aa						422

```
<210> 508
<211> 411
<212> DNA
<213> Homo Sapien
```

```
<220>
<221> misc_feature
<222> (1)...(411)
<223> n=A,T,C or G
```

<400> 508						
atggagacag	gcctcgtg	cttctcctgg	tcgctgtgct	caaagggtgtc	cagtgtcagt	60
cggtggagga	gtccgggggt	cgcctgggtca	cgcctgggac	accctgaca	ctcacctgca	120
cagtctctgg	aatcgacctc	agtagctact	gcctgagctg	ggtccgccag	gctccagggg	180
aggggctgga	atggatcgga	atcattggta	ctcctgggtga	cacatactac	gcgagggtggg	240
cgaaaggccg	attcaccatc	tccaaaacct	cgaccacggt	gcattntgaa	atcncagctc	300
ctgacaaccg	ggacacggcc	acctatttct	gtgccagaga	tcttcgggat	ggtagtagta	360
ctgtttatta	taaaatctgg	ggcccaggca	ccctgggtcac	cgtctccttg	g	411

```
<210> 509
<211> 15
<212> PRT
<213> Artificial Sequence
```

<220>  
<223> Made in a lab

<400> 509  
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser  
1 5 10 15

```
<210> 510
<211> 15
<212> PRT
<213> Artificial Sequence
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&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 510

Pro	Glu	Tyr	Asn	Arg	Pro	Leu	Leu	Ala	Asn	Asp	Leu	Met	Leu	Ile
1				5					10					15

&lt;210&gt; 511

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 511

Tyr	His	Pro	Ser	Met	Phe	Cys	Ala	Gly	Gly	Gly	Gln	Asp	Gln	Lys
1				5					10					15

&lt;210&gt; 512

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 512

Asp	Ser	Gly	Gly	Pro	Leu	Ile	Cys	Asn	Gly	Tyr	Leu	Gln	Gly	Leu
1				5					10					15

&lt;210&gt; 513

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 513

Ala	Pro	Cys	Gly	Gln	Val	Gly	Val	Pro	Asx	Val	Tyr	Thr	Asn	Leu
1				5					10					15

&lt;210&gt; 514

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 514

Leu	Cys	Lys	Phe	Thr	Glu	Trp	Ile	Glu	Lys	Thr	Val	Gln	Ala	Ser
1				5					10					15

&lt;210&gt; 515

<211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 515  
 Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg  
 1 5 10 15

<210> 516  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 516  
 Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln  
 1 5 10 15

<210> 517  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 517  
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met  
 1 5 10 15

<210> 518  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 518  
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly  
 1 5 10 15

<210> 519  
 <211> 17  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 519  
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg Asn Tyr Asp Glu Gly Cys  
 1 5 10 15



Gly

<210> 520  
<211> 25  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 520  
Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr  
1 5 10 15  
Glu Ala Arg Arg His Tyr Asp Glu Gly  
20 25

<210> 521  
<211> 21  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 521  
Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu  
1 5 10 15  
Pro Pro Pro Pro Ala  
20

<210> 522  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 522  
Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr Gly Ser Gln Glu Asp  
1 5 10 15  
Phe Thr Gln Val  
20

<210> 523  
<211> 254  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<220>  
<221> VARIANT  
<222> (1)...(254)  
<223> Xaa = any amino acid

<400> 523  
 Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile  
 1 5 10 15  
 Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile  
 20 25 30  
 Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu  
 35 40 45  
 Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln  
 50 55 60  
 Trp Val Leu Ser Ala Thr His Cys Phe Gln Asn Ser Tyr Thr Ile Gly  
 65 70 75 80  
 Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met  
 85 90 95  
 Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu  
 100 105 110  
 Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu  
 115 120 125  
 Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala  
 130 135 140  
 Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg  
 145 150 155 160  
 Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu  
 165 170 175  
 Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys  
 180 185 190  
 Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser Gly  
 195 200 205  
 Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly  
 210 215 220  
 Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu  
 225 230 235 240  
 Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser  
 245 250

&lt;210&gt; 524

&lt;211&gt; 765

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<400> 524  
 atggccacag caggaaatcc ctggggctgg ttcttgggggt acctcatcct tgggtgtcgca 60  
 ggatcgctcg tctctggtag ctgcagccaa atcataaacg gcgaggactg cagcccgcac 120  
 tcgcagccct ggcaggcggc actgggcatg gaaaacgaat tgttctgtctc gggcgctcctg 180  
 gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg 240  
 ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggg ggaggccagc 300  
 ctctccgtac ggcacccaga gtacaacaga cccttgctcg ctaacgacct catgctcatc 360  
 aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag 420  
 tgccctaccg cggggaactc ttgcctcggt tctggctggg gtctgctggc gaacggcaga 480  
 atgcctaccg tgctgcagtg cgtgaacgtg tccggtgggt ctgaggagggt ctgcagtaag 540  
 ctctatgacc cgctgtacca cccagcatg ttctgcgccg ggggagggca agaccagaag 600  
 gactcctgca acggtgactc tggggggccc ctgatctgca acgggtactt gcagggcctt 660  
 gtgtcttttcg gaaaagcccc gtgtggccaa gttggcgtgc caggtgtcta caccaacctc 720  
 tgcaaattca ctgagtggat agagaaaacc gtccaggcca gttaa 765

&lt;210&gt; 525

&lt;211&gt; 254

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 525

```

Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile
 1          5          10          15
Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile
 20          25          30
Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
 35          40          45
Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
 50          55          60
Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
 65          70          75          80
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
 85          90          95
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
100          105          110
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
115          120          125
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
130          135          140
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
145          150          155          160
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
165          170          175
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
180          185          190
Ala Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly
195          200          205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
210          215          220
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
225          230          235          240
Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
245          250

```

&lt;210&gt; 526

&lt;211&gt; 963

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 526

```

atgagttcct gcaacttcac acatgccacc tttgtgctta ttggtatccc aggattagag 60
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aactgcatcg tggcttccat cgtaaggacg gaacgcagcc tgcacgctcc gatgtacctc 180
tttctctgca tgcttgacgc cattgacctg gccttatcca catccaccat gcctaagatc 240
cttgcccttt tctgggttga ttcccagagag attagctttg aggcctgtct taccagatg 300
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gccagattg gcacgtggc tgtggtccgc ggatccctct tttttttccc actgcctctg 480
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caggatgtaa tgaagtggc ctatgcagac actttgcccc atgtggtata tgggtctact 600
gccattctgc tggctcatggg cgtggacgta atgttcatct ccttgccta ttttctgata 660
atacgaacgg ttctgaact gccttccaag tcagagcggg ccaaggcctt tggaacctgt 720
gtgtcacaca ttggtgtggt actgccttc tatgtgccac ttattggcct ctcaagtgtgta 780
caccgctttg gaaacagcct tcatcccat gtgcgtgttg tcatgggtga catctacctg 840
ctgctgcctc ctgtcatcaa tcccatcatc tatggtgccaa aaaccaaaca gatcagaaca 900
cgggtgctgg ctatgttcaa gatcagctgt gacaaggact tgcaggctgt gggaggcaag 960
tga

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<210> 527

**<211> 320**

<212> PRT

<213> Homo sapiens

**<400> 527**

<400> 527  
Met Ser Ser Cys Asn Phe Thr His Ala Thr Phe Val Leu Ile Gly Ile  
5 10 15

Pro Gly Leu Glu Lys Ala His Phe Trp Val Gly Phe Pro Leu Leu Ser  
20 25 30

Met Tyr-Val Val Ala Met Phe Gly Asn Cys Ile Val Val Phe Ile Val  
35 40 45

Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met  
50 55 60

Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile  
65 70 75 80

Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Phe Glu Ala Cys  
85 90 95

Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr  
100 105 110

Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro  
115 120 125

Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly  
130 135 140

```
Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu  
145                      150                155                    160
```

Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser  
165 170 175

Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu  
180 185 190

Pro	Asn	Val	Val	Tyr	Gly	Leu	Thr	Ala	Ile	Leu	Leu	Val	Met	Gly	Val
		195					200					205			

Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val  
210 215 220

Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys  
225 230 235 240

Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro L u Ile Gly  
245 250 255

Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg  
260 265 270

Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro  
275 280 285

Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala  
290 295 300

Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys  
305 310 315 320

<210> 528  
<211> 20  
<212> DNA  
<213> Homo Sapien

<400> 528  
actatggtcc agaggctgtg

20

<210> 529  
<211> 20  
<212> DNA  
<213> Homo Sapien

<400> 529  
atcacctatg tgccgcctct

20

<210> 530  
<211> 1852  
<212> DNA  
<213> Homo sapiens

<400> 530  
ggcacgagaa ttaaaaccct cagcaaaaaca ggcatagaag ggacatacct taaagtaata 60  
aaaaccacct atgacaagcc cacagccaac ataatactaa atgggggaaaa gttagaagca 120  
tttctcttga gaactgcaac aataaataca aggatgctgg attttgtcaa atgccttttc 180  
tgtgtctgtt gagatgctta tgtgactttg cttttaattc tgtttatgtg attatcacat 240  
ttattgactt gcctgtgtta gaccggaaga gctgggggtgt ttctcaggag ccaccgtgtg 300  
ctgcggcagc ttccgggataa cttgaggctg catcactggg gaagaaacac aytccgtgtc 360  
gtggcgctga tggctgagga cagagcttca gtgtggcttc tctgcgactg gcttcttcgg 420  
ggagttcttc cttcatagtt catccatatg gctccagagg aaaattatat tattttgtta 480  
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 <213> Homo sapiens

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 <213> Homo sapiens

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Val Lys Thr Leu Gly Ser Lys Arg Cys Lys Trp Cys Cys His Cys Phe
      35                                40                    45

Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val Val Ala Trp Gly Asp
      50                                55                    60

Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr His Val His Gly Glu
      65                                70                    75                    80

Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg
      85                                90                    95

Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Arg Asp
      100                               105                    110

Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser
      115                               120                    125

Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys Gln Leu Asn Val Leu

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130 135 140

Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala Val Gln Cys Gln Glu  
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Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile  
165 170 175

Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Val Tyr Asn Glu  
180 185 190

Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu  
195 200 205

Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Ile His Glu  
210 215 220

Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu  
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Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys  
245 250 255

Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu Glu Gln Asn Val Asp  
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<213> Homo sapiens

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&lt;400&gt; 534

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Leu Gln Ser Met Pro Gln Gly Ser Tyr Ala Thr Ala Arg Phe Leu Val  
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Ala Lys Arg Pro Thr Thr Gly His Leu Glu Lys Glu Phe Met Phe His  
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Cys Arg Lys Gln Pro Gly Ser Pro Ser Arg Gly Leu Gly Leu Leu Trp  
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Pro Trp Pro Asp Ile Glu Phe Val Pro Arg Gln Asp Lys Leu Thr Gln  
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Ser Ser Val Leu Val Pro Gln Ile Cys Ala Cys Gln Thr Arg Pro Asn  
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Trp Leu Asn Glu Gln Pro Ala Thr Ser Ala Gly Val Arg Leu Glu Glu  
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Val Asp Gln Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys  
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Ser His Ser Leu Ser Gly Cys His Leu Met Ala Asp Ile Ala Lys Ala  
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Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr  
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Asp Val Pro Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser  
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Ser Trp His Thr Leu Ala Glu Val Thr Gly Cys Ser Leu Ser Pro Leu  
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Trp Ser His Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr  
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Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu  
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&lt;210&gt; 535

&lt;211&gt; 6082

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens



&lt;400&gt; 535

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&lt;213&gt; Homo sapiens

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&lt;223&gt; n=A,T,C or G

&lt;400&gt; 536

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&lt;210&gt; 537

&lt;211&gt; 1228

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 537

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5

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25

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Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser		
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Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro		
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Ser His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln		
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Gln Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly		
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Lys Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala		
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Leu Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile		
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Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn		
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Leu Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp		
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Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu		
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Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val Thr His		
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Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp		
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 35 40 45  
 Tyr Leu Val Leu Gly Ile Phe Thr Leu Ile Glu Glu Ser Ala Lys Val  
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 Val Leu Thr Phe Cys Thr Leu Ile Leu Ala Ile Leu His His Leu Tyr  
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 Lys Thr Leu Asp Ala Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu

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Val	Leu	Leu	Gln	Asn	Lys	Glu	Ser	Leu	Phe	Tyr	Lys	Met	Val	Gln	Gln
			1220					1225					1230		
Leu	Gly	Lys	Ala	Glu	Ala	Ala	Ala	Leu	Thr	Glu	Thr	Ala	Lys	Gln	Arg
		1235					1240					1245			

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1250 1255 1260

<210> 539  
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<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

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1 5 10

<210> 540  
<211> 9  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

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<210> 541  
<211> 14  
<212> PRT  
<213> Homo sapiens

<400> 541  
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<210> 542  
<211> 15  
<212> PRT  
<213> Homo sapiens

<400> 542  
Thr Gln Val Val Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala  
5 10 15

<210> 543  
<211> 12  
<212> PRT  
<213> Homo sapiens

<400> 543  
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Met Thr

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<210> 545
<211> 18
<212> PRT
<213> Homo sapiens
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Ser Val

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<210> 546
<211> 29
<212> PRT
<213> Homo sapiens
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Thr Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg Met  
20 25

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<210> 547
<211> 58
<212> PRT
<213> Homo sapiens
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Ser Ala Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu  
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Cys Arg Met Pro Arg Thr Leu Arg Arg Leu  
50 55

200

<210> 548  
<211> 18  
<212> PRT  
<213> Homo sapiens

<400> 548  
Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu  
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Glu Cys

<210> 549  
<211> 18  
<212> PRT  
<213> Homo sapiens

<400> 549  
Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg  
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Gln Ala

<210> 550  
<211> 14  
<212> PRT  
<213> Homo sapiens

<400> 550  
Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe  
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<210> 551  
<211> 11  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 551  
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<210> 552  
<211> 2577  
<212> DNA  
<213> Homo sapiens

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tcataccagt ccacggacta ttatgaacca caccacacag gaggaggtga gcactaggca 180  
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&lt;210&gt; 553

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 553

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Ser Ile Cys Asn Met Thr Cys Ala Ser Val Phe Phe Cys Asp Gln Lys
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Phe Leu Thr Phe Ser Phe Leu Ser Met Val Glu Pro Pro Arg Ala Gly
          20                      25                      30

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Val Leu Asn Ser Gln Ala Thr Asp Ser Tyr Gln Ser Thr Asp Tyr Tyr
          35                      40                      45

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Glu Pro His His Thr Gly Gly Gly Glu His
          50                      55

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&lt;210&gt; 554

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 554

Leu Gln Lys Asn Lys Leu Arg Ala Ser Thr Asp Ser Thr Leu Trp Ile  
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Cys Ala Ala Glu Ala Ser Thr Lys Pro Tyr Phe Tyr Thr Cys Leu Val  
                                   20                                  25                                  30

Met Leu His Gly Gln Gly Leu Ala Leu Leu Ser Pro Thr Asn Leu Pro  
                   35                                  40                                  45

Glu Ile Leu Arg Phe Leu Phe Asn Gly Phe Leu  
           50                                  55

&lt;210&gt; 555

&lt;211&gt; 71

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 555

Leu Gly Arg Phe Ser Leu Ser Cys Lys Ser Gly His Ser Arg Gly Gln  
                                   5                                  10                                  15

Pro Gln Leu Gly Ala Thr Ala Gln Gly Lys Val His Met Gly Leu Ser  
                                   20                                  25                                  30

Thr Ala Gln Gly Ser Ile Gln Asp Ile Lys Val Pro His Ser Ile Asp  
                   35                                  40                                  45

Leu Val Ala Lys Lys Lys Lys Gln Thr Leu Ile Ser Phe Cys His Pro  
           50                                  55                                  60

Ser Asp Pro Leu Glu Leu Leu  
       65                                  70

&lt;210&gt; 556

&lt;211&gt; 81

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 556

Asn His Pro Glu Gln Gly Ser Ser Thr Pro Arg Pro Gln Thr His Thr  
                                   5                                  10                                  15

Ser Pro Arg Thr Ile Met Asn His Thr Thr Gln Glu Glu Val Ser Thr  
                   20                                  25                                  30

Arg Gln Ala Lys Glu Ala Ser Pro Val Leu Thr Ala Thr Arg His Gly  
                   35                                  40                                  45

Ser Tyr Tyr Ser Leu Asn Ser Ala Ser Thr Gln Ile Ser Asp Asn Ile

203

50                      55                      60  
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 Ile

<210> 557  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens

<400> 557  
 Ser Leu Ser Ala Thr Pro Leu Thr Leu Trp Asn Ser Ser Asp Pro Leu  
                                  5                      10                      15

Glu Gln Ala Tyr Leu Ile Ser Ala Arg Glu Lys Thr Asn Asn Gly Leu  
                                  20                      25                      30

Lys Gly Ser Leu Thr Met Lys Val Ser Ala Asn Ser Trp Leu Arg Cys  
                                  35                      40                      45

Gly Phe His Ile Arg Phe  
                                  50

<210> 558  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<220>  
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 <222> (1)...(77)  
 <223> Xaa = Any amino acid

<400> 558  
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Ile Tyr Phe Thr Asn Leu Thr Ser Cys Leu Ser Val Gln Asn Gln Thr  
                                  20                      25                      30

Phe Thr Cys Thr Lys Arg His Lys His Leu Gln Cys Ser Ser Val His  
                                  35                      40                      45

Leu Cys Lys Ile Pro Pro Arg Leu Lys Gly Arg Asp Lys Lys Lys Lys  
                                  50                      55                      60

Pro Ser Tyr Leu Ser Gly Val Leu His Ser Arg Ser Tyr  
                                  65                      70                      75

<210> 559  
 <211> 50  
 <212> PRT

<213> Homo sapiens

<400> 559

Thr Leu Pro Pro Leu Arg Ser Val Ile Thr Leu Glu Thr His Trp Ser  
5 10 15

Thr Asn Pro Val Val Asn Cys Leu Ser Glu Gly Ser Arg Leu Cys Ala  
20 25 30

Ser Tyr Glu Asn Leu Met Pro Asp Asp Leu Ser Leu Ser His Phe Ala  
35 40 45

Pro Arg  
50

<210> 560

<211> 56

<212> PRT

<213> Homo sapiens

<400> 560

Ile Gly Ser Leu Lys Gly Pro Thr Thr Ala Gly Ser His Cys Ser Gly  
5 10 15

Glu Gly Ser Tyr Gly Thr Phe Tyr Cys Pro Arg Phe Tyr Thr Gly Tyr  
20 25 30

Lys Gly Ala Ser Gln Tyr Arg Ser Gly Ser Lys Glu Glu Glu Thr Asn  
35 40 45

Thr Asp Leu Phe Leu Pro Pro Leu  
50 55

<210> 561

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 561

Val Leu His Leu Asp Gln Met Asn Asn Val Gly Ile Xaa Met Asp Lys  
5 10 15

Gly Leu Lys Ser Pro Glu Ile Lys Asn Pro Ala Pro Thr Gly Thr Ser  
20 25 30

Asn Leu Ser Cys Phe Leu Ser Xaa Phe Trp Leu Met Gln Gly Thr Asn  
35 40 45

Ser Leu Pro Arg Glu Asn Tyr Leu Asn  
50 55

205

<210> 562  
<211> 59  
<212> PRT  
<213> Homo sapiens

<220>  
<221> VARIANT  
<222> (1)...(59)  
<223> Xaa = Any amino acid

<400> 562  
Asp Leu Tyr Pro Xaa Arg Ser Gln His Cys Ser Phe Asp Pro Ser Val  
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Ala Pro Met His Gly Ile Lys Asn Ser Ile Thr Ser Leu Ile Phe Leu  
                  20                  25                  30  
  
Ile Ser Tyr Leu Xaa Leu Glu Met Ser Ser Leu Ser Glu Ser Leu Val  
          35                  40                  45  
  
Leu Ser Ser Gly Asp Tyr Val Leu Asp Thr Pro  
      50                  55

<210> 563  
<211> 79  
<212> PRT  
<213> Homo sapiens

<400> 563  
Cys Phe Leu Phe Pro Tyr Leu Trp Leu Tyr Ala Gln Pro Leu Phe Pro  
                  5                  10                  15  
  
Lys Gln Gln Pro Pro Ala Leu Ala Pro Gly His Pro Asp Phe Ile His  
                  20                  25                  30  
  
Thr Gln Asn Glu Gln Ile Asp Pro Ser Pro His Ile Gln Asn Leu Met  
          35                  40                  45  
  
Trp Asn Pro His Leu Ser Gln Glu Leu Ala Glu Thr Phe Met Val Arg  
      50                  55                  60  
  
Asp Pro Leu Arg Pro Leu Leu Val Phe Ser Leu Ala Asp Ile Arg  
      65                  70                  75

<210> 564  
<211> 64  
<212> PRT  
<213> Homo sapiens

<400> 564  
Ala Cys Ser Lys Gly Ser Glu Glu Phe Gln Arg Val Arg Gly Val Ala  
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Glu Arg Asp Gln Cys Leu Phe Leu Leu Leu Cys Tyr Gln Ile Tyr Thr  
      20                  25                  30

Val Arg His Leu Tyr Il Leu Tyr Arg Thr Leu Gly Ser Arg Lys Ser  
35 40 45

His Met Asn Leu Pro Leu Ser Ser Gly Ser Gln Leu Trp Leu Ala Pro  
50 55 60

<210> 565

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 565

Leu Tyr Tyr Cys Ser Tyr Leu Cys His Phe Arg Thr Ala Leu Ile Leu  
5 10 15

Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln  
20 25 30

Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu  
35 40 45

Tyr Ala Val Ser Ser Xaa His Asn Val  
50 55

<210> 566

<211> 55

<212> PRT

<213> Homo sapiens

<400> 566

Ile Leu Leu Glu Phe Phe Arg Asn Gln Arg Gly Ser Leu Asn Pro Arg  
5 10 15

Lys Thr Val Pro Phe Ile Lys Ser Glu Gly Gly Glu Lys Lys Gly His  
20 25 30

Cys Asn His Ser Val Val Ser Ile Asp Ser Ala Ala Ala Leu Leu Pro  
35 40 45

Leu Lys Leu Val Leu Leu Pro  
50 55

<210> 567

<211> 51

<212> PRT

<213> Homo sapiens

<400> 567

Tyr Ser Asp Phe Asp Val Phe Cys Ser His Thr Tyr Gly Tyr Met Leu

207

5 10 15  
 Ser His Cys Ser Gln Ser Ser Ser Pro Leu Leu Trp Pro Leu Gly Ile  
 20 25 30  
 Leu Thr Leu Ser Thr His Lys Met Ser Lys Leu Thr Leu Pro Pro Ile  
 35 40 45  
 Phe Arg Thr  
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<210> 568  
 <211> 75  
 <212> PRT  
 <213> Homo sapiens

<400> 568  
 Lys Val Gly Glu Tyr Ile Leu Gln Ser Leu Leu Arg Ile Arg Lys Ile  
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 Tyr Val Ala Phe Asn Ser Val Pro Ser Thr Cys Leu Leu Ala Ser Leu  
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 Thr Glu Thr Pro Val Thr Thr Ile Leu Thr Ile Ile Ile Asn Leu Thr  
 35 40 45  
 Cys Phe Gln His Ala Glu Ser Ser Tyr Leu Phe Tyr Pro Leu Ala Asp  
 50 55 60  
 Phe Leu Leu Gln His Ile Ser Leu Gly Lys Leu  
 65 70 75

<210> 569  
 <211> 4809  
 <212> DNA  
 <213> Homo sapiens

<400> 569  
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atgagatgca	aagggcagtg	gacaaggagc	caaggagggt	ggctctagtc	acgctgggtat	4380
ggtgccagct	tgaggatgct	gggcaagtcc	cgagccgtct	gccttcttag	taccacagtt	4440
accactgtct	gttacctcgc	gagttcaagt	gcttcacgtg	agacagctac	gagacaggcc	4500

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cctggaaact ggaaaaatgcy aagtaaatgt catgcacaat tgttggtcac attttatctc 4560
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ttgttccttg aaatgactca gagacatttt ctgaattggc ttccatcagc caagcatttc 4680
ttcagaactg gaaaaatgct ttaaatttgg ctttgtcatg attattaaaa cactctgtac 4740
attttttatt attgaaatta acacattgcc tactttttaa aaattggaaa aagaaaaaaa 4800
aaaaaaaaa 4809

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&lt;210&gt; 570

&lt;211&gt; 951

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 570

```

aaaattgaat attgagatac cattcttttag tgttaccttt tttaccacac tgtgtttctg 60
aaaatattgg aattttattc atcttaaaaa ttggaccggg ccttatttac catctttaat 120
ccatttttagt actatgggtg agtacatgga attgaagtct ggcttaaate ttcagaaagt 180
tatatatcta ttttatttta tttttttgag acagagtctc gctgtgtcac ccaggctgga 240
gtgcggtgcc acaatcttgg ctcaactgcaa cctctgagtc ccaggttcaa gcgatactca 300
tgccctcgcc tcctgagtag ctgggactac aggcgtgcac caccacatct ggctaattct 360
tttttgtatt tttagtagag acgggggttc actgtgggtc ccatctcctg acctcgtgat 420
ccgcctgcct cccaaagtgc tgggattaca ggcatgagcc accgcacaca gctgggactg 480
ggtaatttat aaagaaaaga ggtttaatga ctacagttc cgcattggct gagaggctc 540
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&lt;210&gt; 571

&lt;211&gt; 819

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 571

```

cagcttaaaa atgggtttctt gaaatcagtg attagcattc actcaccagt acccctacta 60
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acttgtccta ttgtctttta atttctgcct gttctttatg gctttcaact tcataaataa 420
catgttttct caaatctctt tgtgaattcc agagagggcc aggcacggtg gctcacatct 480
gtaatcccag cactttgggg aggctgagac gggtgatca cttgaggtca ggagtttgag 540
accagcctgg ccaacatggt gaaatcccgt ttcactaaaa atacaaaaat taccaggga 600
tggtggcggg cgctgtaat cccaggctact cgggaggctg agggaggaga atcgcttgaa 660
cctgggaggc tgagggagga gaatcgcttg aaccggggag gcagagggtg cagtgaaccg 720
agatcatggt gctgcactcc agcctggtca acagagcaag actctgcctc aaaaacaaac 780
aaataaacaa acaaacaaac aaaacagaga gattttgct 819

```

&lt;210&gt; 572

&lt;211&gt; 203

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 572

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tatagaatac tcaagctatg catcaagctt ggtaccgagc tcggatccac tatttaacggc 60

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<210> 573
<211> 132
<212> PRT
<213> Homo sapiens
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<400> 573
Met Val Glu Gly Glu Gly Glu Ala Arg His Val Leu His Gly Gly Arg
      5                               10                      15

Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg
      20                                25                      30

Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu
      35                                40                      45

Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu
      50                                55                      60

Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala
      65                                70                      75                      80

Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly
      85                                90                      95

Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro
      100                             105                      110

Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile
      115                             120                      125

Leu Leu Asn Tyr
      130
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<210> 574
<211> 62
<212> PRT
<213> Homo sapiens
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<400> 574  
Met Thr His Ser Ser Ala Trp Leu Glu Arg Pro Gln Glu Thr Tyr Asn  
5 10 15  
His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln  
20 25 30  
Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu  
35 40 45  
Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala  
50 55 60

**<210> 575**

211

<211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 575  
 Met Val Lys Ser Arg Phe Thr Lys Asn Thr Lys Ile Thr Gln Ala Trp  
                             5                            10                            15  
 Trp Arg Ala Pro Val Ile Pro Gly Thr Arg Glu Ala Glu Gly Gly Glu  
                             20                            25                            30  
 Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly  
                             35                            40                            45  
 Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp  
                             50                            55                            60  
 Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys  
                             65                            70                            75

<210> 576  
 <211> 68  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> (1)...(68)  
 <223> Xaa = Any Amino Acid

<400> 576  
 Met Leu Gly Lys Ser Arg Ala Val Cys Leu Pro Ser Thr Thr Val Thr  
                             5                            10                            15  
 Thr Val Cys Tyr Leu Ala Ser Ser Ser Ala Ser Arg Glu Thr Ala Thr  
                             20                            25                            30  
 Arg Gln Ala Pro Gly Asn Trp Lys Met Xaa Ser Lys Cys His Ala Gln  
                             35                            40                            45  
 Leu Leu Phe Thr Phe Tyr Leu Asn His Phe Tyr Gln Ile Arg Leu Asn  
                             50                            55                            60  
 Pro Gly Tyr Ser  
 65

<210> 577  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<400> 577  
 Met Tyr Leu Glu Asn Ser Phe Tyr Cys Gln Met Ile Leu Leu Lys Arg  
                             5                            10                            15  
 Cys Arg Leu Ser Lys Ile Ser Thr Gln Arg Val Val Pro Asp Gly Pro

212

20 25 30

Pro Ala Pro Val Pro Gly Ser Phe Pro Met Phe Pro Arg Phe Gly Phe  
35 40 45

Arg Leu Ala Pro Pro Ala Asp Thr Pro  
50 55

<210> 578  
<211> 51  
<212> PRT  
<213> Homo sapiens

<400> 578  
Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu Leu Tyr Ile Arg His  
5 10 15

His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr Lys Lys Leu Asn Tyr  
20 25 30

Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His Ile Ala Lys Val Tyr  
35 40 45

Gln Pro His  
50

<210> 579  
<211> 56  
<212> PRT  
<213> Homo sapiens

<400> 579  
Met His Phe Thr Phe Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu  
5 10 15

Leu Tyr Ile Arg His His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr  
20 25 30

Lys Lys Leu Asn Tyr Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His  
35 40 45

Ile Ala Lys Val Tyr Gln Pro His  
50 55

<210> 580  
<211> 67  
<212> PRT  
<213> Homo sapiens

<400> 580  
Met Glu Leu Arg Thr Lys Ala Leu Arg Thr Ala Gln Gln Leu Thr Ser  
5 10 15

Cys Val Thr Ala Leu Lys Ala Ala Gly Pro Pro Leu Thr Phe Trp Lys  
20 25 30

Gly Lys Trp Val Gln Cys Cys Leu Pro Leu Trp Gly Leu Leu Gly Ser  
                   35                                  40                                  45

His Ala Phe Tyr Ile Tyr Ala Val Asp Ile Phe Met Phe Pro Gly Ser  
           50                                  55                                  60

Phe Ile His  
   65

<210> 581

<211> 77

<212> PRT

<213> Homo sapiens

<400> 581

Met Leu Glu Val Lys Phe Glu Val Ser Leu Arg Pro Thr Gly Asn Glu  
                                   5                                  10                                  15

Thr Ala Gly Gln Thr His Gly Thr Gln Asp Lys Gly Ser Lys Asp Ser  
                   20                                  25                                  30

Thr Ala Ala Asp Ile Leu Cys Asp Ser Leu Glu Ser Ser Arg Pro Ala  
           35                                  40                                  45

Ala His Ile Leu Glu Gly Lys Met Gly Thr Met Leu Ser Ala Thr Leu  
           50                                  55                                  60

Gly Pro Ser Trp Val Thr Cys Ile Leu His Leu Cys Ser  
   65                                  70                                  75

<210> 582

<211> 51

<212> PRT

<213> Homo sapiens

<400> 582

Met Leu Phe Leu Gln Thr Ile Asp Thr Lys Cys Thr Gly Ile Glu Ile  
                                   5                                  10                                  15

Asn Arg Asn Trp Ser Lys Val Trp His Thr His Ser His Val Asp Val  
           20                                  25                                  30

Lys Leu Cys Leu Glu Phe Leu Cys Gly Val Trp Phe Gly Leu Gly Phe  
           35                                  40                                  45

Leu Gly Val  
   50

<210> 583

<211> 60

<212> PRT

<213> Homo sapiens

<400> 583

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
5 10 15

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
20 25 30

Arg Thr Leu Thr Ser' Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
35 40 45

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
50 55 60

<210> 584

<211> 76

<212> PRT

<213> Homo sapiens

**<400> 584**

Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
5 10 15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
20 25 30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
35 40 45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
50 55 60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
65 70 75

**<210> 585.**

<211> 50

<212> PRT

**<213> Homo sapiens**

**<400> 585**

Met Val Tyr Arg Phe Gly Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu  
5 10 15

Ala Ser Leu Gly Ser Ser Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp  
20 25 30

Arg Gln Ala Asp Pro Ser Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu  
35 40 45

Leu Phe  
50

**<210> 586**

**<211> 60**

<212> PRT

**<213> Homo sapiens**

<400>	587						
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agcccccccg	gtgaagctcg	ctgctttccc	tacctcctta	agtgactgcc	aaacgcccac	120	
cggctggaat	tgctctgggt	atgatgacag	agaaaatgat	ctcttcctct	gtgacaccaa	180	
cacctgtaaa	tttgatgggg	aatgtttaag	aattggagac	actgtgactt	gcgtctgtca	240	
gttcaagtgc	aacaatgact	atgtgcctgt	gtgtggctcc	aatggggaga	gctaccagaa	300	
tgagtgttac	ctgcgacagg	ctgcatgcaa	acagcagagt	gagatacttg	tggtgtcaga	360	
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agaaactagt	caaaaaggaga	catccacctg	tgatatattg	cagtttggtg	cagaatgtga	480	
cgaagatgcc	gaggatgtct	ggtgtgtgtg	taatattgac	tgttctcaaa	ccaacttcaa	540	
tccccctctgc	gcttctgatg	ggaaatctta	tgataatgca	tgccaaatca	aagaagcatc	600	
gtgtcagaaa	caggagaaaa	ttgaagtcac	gtctttgggt	cgatgtcaag	ataacacaac	660	
tacaactact	aagtctgaag	atgggcatca	tgcaagaaca	gattatgcag	agaatgctaa	720	
caaattagaa	gaaagtgcc	gagaacacca	cataccttgt	ccggaacatt	acaatggctt	780	
tgcatgcat	gggaagtgtg	agcattctat	caatatgcag	gagccatctt	gcaggtgtga	840	
ctgtggttat	actggacaac	actgtgaaaa	aaaggactac	agtgttctat	acgttgttcc	900	
cggctctgta	cgatttcagt	atgtcttaat	cgcagctgtg	attggaacaa	ttcagattgc	960	
tgtcatctgt	gtggtgggtc	tctgcatcac	aaggaaatgc	cccagaagca	acagaattca	1020	
cagacagaag	caaaatacag	ggcactacag	ttcagacaat	acaacaagag	cgcccacgag	1080	
gttaatctaa	agggagcatg	tttcacagtg	gctggactac	cgagagcttg	gactacacaa	1140	
tacagtatta	tagacaaaag	aataagacaa	gagatctaca	catgttgctt	tgcatattgtg	1200	
gtaatctaca	ccaatgaaaa	catgtactac	agctatatatt	gattatgtat	ggatatattt	1260	
gaaatagtat	acattgtctt	gatgtttttt	ctgtaattga	aataaactat	ttatatcaca	1320	
caatawagtt	ttttctttcc	catgtatttg	ttatatataa	taaatactca	gtgatgagaa	1380	
aaaaaaaaaa	aaaaaaaaaa	rwmgaccc				1408	

<400> 588  
Met Pro Gln Lys Gln Gln Asn Ser Gln Thr Glu Ala Lys Tyr Arg Ala  
5 10 15  
Leu Gln Phe Arg Gln Tyr Asn Lys Ser Val His Glu Val Asn Leu Lys  
20 25 30

216

Gly Ala Cys Phe Thr Val Ala Gly Leu Pro Arg Ala Trp Thr Thr Gln  
           35                  40                  45  
 Tyr Ser Ile Ile Asp Lys Arg Ile Arg Gln Glu Ile Tyr Thr Cys Cys  
           50                  55                  60  
 Leu Ala Phe Val Val Ile Tyr Thr Asn Glu Asn Met Tyr Tyr Ser Tyr  
           65                  70                  75                  80  
 Ile

<210> 589  
 <211> P57  
 <212> PRT  
 <213> Homo sapiens

<400> 589  
 Met Thr Met Cys Leu Cys Val Ala Pro Met Gly Arg Ala Thr Arg Met  
                   5                  10                  15  
 Ser Val Thr Cys Asp Arg Leu His Ala Asn Ser Arg Val Arg Tyr Leu  
                   20                  25                  30  
 Trp Cys Gln Lys Asp His Val Pro Gln Met Gln Asp Gln Asp Leu Glu  
                   35                  40                  45  
 Met Glu Ser Met Lys Ala Leu Glu Lys Leu Val Lys Arg Arg His Pro  
           50                  55                  60  
 Pro Val Ile Phe Ala Ser Leu Val Gln Asn Val Thr Lys Met Pro Arg  
           65                  70                  75                  80  
 Met Ser Gly Val Cys Val Ile Leu Thr Val Leu Lys Pro Thr Ser Ile  
                   85                  90                  95  
 Pro Ser Ala Leu Leu Met Gly Asn Leu Met Ile Met His Ala Lys Ser  
                   100                  105                  110  
 Lys Lys His Arg Val Arg Asn Arg Arg Lys Leu Lys Ser Cys Leu Trp  
           115                  120                  125  
 Val Asp Val Lys Ile Thr Gln Leu Gln Leu Leu Ser Leu Lys Met Gly  
           130                  135                  140  
 Ile Met Gln Glu Gln Ile Met Gln Arg Met Leu Thr Asn  
           145                  150                  155

<210> 590  
 <211> 347  
 <212> PRT  
 <213> Homo sapiens

<400> 590  
 Met Leu Leu Ile Val Ala Arg Pro Val Lys Leu Ala Ala Phe Pro Thr  
                   5                  10                  15

Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys Ser Gly Tyr  
 20 25 30  
 Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn Thr Cys Lys  
 35 40 45  
 Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr Cys Val Cys  
 50 55 60  
 Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly Ser Asn Gly  
 65 70 75 80  
 Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala Cys Lys Gln  
 85 90 95  
 Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala Thr Asp Ala  
 100 105 110  
 Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly Glu Thr Ser  
 115 120 125  
 Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly Ala Glu Cys  
 130 135 140  
 Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile Asp Cys Ser  
 145 150 155 160  
 Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys Ser Tyr Asp  
 165 170 175  
 Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln Glu Lys Ile  
 180 185 190  
 Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr Thr Thr Thr  
 195 200 205  
 Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala Glu Asn Ala  
 210 215 220  
 Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro Cys Pro Glu  
 225 230 235 240  
 His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His Ser Ile Asn  
 245 250 255  
 Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His  
 260 265 270  
 Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val  
 275 280 285  
 Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile  
 290 295 300  
 Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg  
 305 310 315 320



Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser  
 325 330 335

Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile  
 340 345

<210> 591  
 <211> 565  
 <212> DNA  
 <213> Homo sapien

<400> 591  
 actaaagcaa atgaacaagc tgacttgcta gtatcatctg cattcattga agcacaagaa 60  
 cttcatgctt tgactcatgt aaatgcaata ggattaaaaa ataaatttga tatcacatgg 120  
 aaacagacaa aaaatattgt acaacattgc acccagtgtc agattctaca cctggccact 180  
 caggaagcaa gagttaatcc cagaggtcta tgcctaattg tgttatggca aatggatgtc 240  
 atgcacgtac cttcatttgg aaaattgtca tttgtccatg tgacagttga tacttattca 300  
 catttcatat gggcaacctg ccagacagga gaaagtactt cccatgttaa aagacattta 360  
 ttatcttgtt ttcctgtcat gggagttcca gaaaaagtta aaacagacaa tgggccagggt 420  
 tactgtagta aagcatttca aaaattctta aatcagtggg aaattacaca tacaatagga 480  
 attctctata attcccaagg acaggccata attgaaggaa ctaatagaac actcaaagct 540  
 caattgggta aacaaaaaaa aaaaa 565

<210> 592  
 <211> 188  
 <212> PRT  
 <213> Homo sapien

<400> 592  
 Thr Lys Ala Asn Glu Gln Ala Asp Leu Leu Val Ser Ser Ala Phe Ile  
 1 5 10 15  
 Glu Ala Gln Glu Leu His Ala Leu Thr His Val Asn Ala Ile Gly Leu  
 20 25 30  
 Lys Asn Lys Phe Asp Ile Thr Trp Lys Gln Thr Lys Asn Ile Val Gln  
 35 40 45  
 His Cys Thr Gln Cys Gln Ile Leu His Leu Ala Thr Gln Glu Ala Arg  
 50 55 60  
 Val Asn Pro Arg Gly Leu Cys Pro Asn Val Leu Trp Gln Met Asp Val  
 65 70 75 80  
 Met His Val Pro Ser Phe Gly Lys Leu Ser Phe Val His Val Thr Val  
 85 90 95  
 Asp Thr Tyr Ser His Phe Ile Trp Ala Thr Cys Gln Thr Gly Glu Ser  
 100 105 110  
 Thr Ser His Val Lys Arg His Leu Leu Ser Cys Phe Pro Val Met Gly  
 115 120 125  
 Val Pro Glu Lys Val Lys Thr Asp Asn Gly Pro Gly Tyr Cys Ser Lys  
 130 135 140  
 Ala Phe Gln Lys Phe Leu Asn Gln Trp Lys Ile Thr His Thr Ile Gly  
 145 150 155 160  
 Ile Leu Tyr Asn Ser Gln Gly Gln Ala Ile Ile Glu Gly Thr Asn Arg  
 165 170 175  
 Thr Leu Lys Ala Gln Leu Val Lys Gln Lys Lys Lys  
 180 185

<210> 593  
 <211> 271

<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(271)  
 <223> n = A,T,C or G

<400> 593  
 actttatggt cnagtgcana aancncctg gattgccacc ntactctcag ggctgtgant 60  
 tgtgcnccca nagcaacctg ggcaacgagg gacagggggg ccnacaattg agggagcggg 120  
 gtccctagct ggggtctata catgncnggg naagggcngc tgagtnccat nagcaaagga 180  
 nctagnatnt gcgggggtgc ggctggggc taccctttna agcatccntn gatccactcc 240  
 angaancgng gggtagncag gtttnccaac a 271

<210> 594  
 <211> 376  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(376)  
 <223> n = A,T,C or G

<400> 594  
 cctttggggg nggggggaac ctttaccatt gtncaccttt atttcatttg gttnggggttc 60  
 gcgcccctnn gggccaacaa agttatcgtn nttgaagaga anattttttt ggnttngncc 120  
 cgattaagcg ncaaattgtgt agcaaaangc cgtgccactt gtggcgtagc tncgtcgggt 180  
 cgattcgacg acaaggcgtn gcgcgntanc gttagtctcn aatngaccn gtggcatgag 240  
 cccacgangg ntctgtgtcg tcacatggnc tctagacata acgcnccn ttttttncag 300  
 agggggntgc cgcccttagg gaggnagggg tggggacact agccaancca nantctnacc 360  
 ccattgaaga aaaggn 376

<210> 595  
 <211> 242  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(242)  
 <223> n = A,T,C or G

<400> 595  
 agnctgctgn tcgtnccctn tatgtggctt catnntgagg acaanagtng cactgagget 60  
 tgnnatgcc aggcaaggnc aagctggctc aaaaagcacc caccacctc tagnaanggt 120  
 atgccangag cangtgcacc agtcccaact angagnccn ggcatgntac atcttcttcc 180  
 acccctnaaa ntttngngta caangnccat ttttcttttt ctcttaaggg ncnctnggct 240  
 tc 242

<210> 596  
 <211> 535  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature

&lt;222&gt; (1)...(535)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 596

accagttgga	tactgctaaa	nagatattta	tgcagcctca	tatgttaagt	cgtatatttt	60
gaaagctttt	taaatttttt	ctttaagaag	attttagatg	cttatcactg	agtaccagag	120
ggatgtaggc	tgatgccctt	atcaacaaag	tcagggactg	tggcacacaa	ggattgacta	180
ctgcagacac	ggccacaatg	ctacctctag	agggcctgaa	tccccctgcc	ctctctggtg	240
gggagaaggg	ctggcagagc	cattagcatg	ggctccggcc	aatcctggcc	actttgacac	300
tcctggtgct	gacccagggg	cctggaggaa	gggatgaggt	gggcagtaga	gatgctcagg	360
gcagtggccc	ctttccatcc	acactggaac	tatttcagta	ttttaccacc	aattcagcca	420
ttcccttggtg	cgttggtgta	acatcagccc	tgctccaggt	ctcagtttcc	cctttgtaaa	480
gggaaagctc	tggattcagg	gagtgatgaa	gaggtcatca	tggctctgag	aattc	535

&lt;210&gt; 597

&lt;211&gt; 257

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(257)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 597

ttttnatacc	caaaantacc	ccatattang	accanacatt	tgtctnggaa	aaattaccat	60
tntntaactt	ttgggccacc	tgagannaaa	tggtgtgaat	ncatgataag	atggancagn	120
attnctctta	agatnngatn	agaccccggt	tttcacggaa	catatccaag	nacccaatag	180
gnaacaagcc	acggngggag	tcacaaacat	atattcttta	ctctcataat	ccgtnnacaa	240
naactnttgn	acttgac					257

&lt;210&gt; 598

&lt;211&gt; 222

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(222)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 598

nntggntacc	gtcnaaaactt	nncttggtac	ccgagctcgg	atccactagt	ccagtgtggt	60
ggaattccat	tgtgttgggc	tataagctgt	aatagtggag	ncgtgctngg	ttcattgcan	120
nagnccctcc	gcanncacnc	ttggnacaac	ctgtgagnag	gcnataaatt	attcacataa	180
tcatcactgc	atgaantcga	ctcaaacgca	tccacntaca	cc		222

&lt;210&gt; 599

&lt;211&gt; 238

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(238)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 599

gcatgacatc	ancgatgtnt	ttggnnacct	ganattngct	aaaactngng	natgccgggn	60
atgnagggtt	ggtantgatc	tatgcaactc	catctcatgg	ggacgtttca	tgtggagtgn	120
tcgacaangt	tgctgnancn	gagaagtgat	gatctcagtt	gaaagggtca	tgtgaatata	180
cnttacactt	gaaaaagaag	cacattggga	atatcacgaa	acgnccacca	acatcctg	238

&lt;210&gt; 600

&lt;211&gt; 232

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(232)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 600

cgaactat	ttt	agactaccta	ggaaaattat	tttagtatca	gaagaatata	aggggtgtag	60
tactcatcag	agctaaatga	gagcgcttta	aaaatgttag	tttgtcttcc	gccatttcta		120
cagaaagctg	caatttcagg	ttttcaacct	aatagggtgat	atttaanaaa	aaaaaaaagc		180
aatcgcaa	aat	agccccactg	cttttataaa	tcattttttc	cccaacacaa	tg	232

&lt;210&gt; 601

&lt;211&gt; 547

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(547)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 601

cattgtgttg	gggaaaaaat	gatttgtata	agcagtgggg	ctatttgcca	ttgctttttt	60
tttttcttaa	atatcaccta	ttaggttgaa	aacctgaaat	tgcagctttc	tgtagaaatg	120
gcggaagaca	aactaacatt	tttaaagcgc	tctcatttag	ctctgatgag	tactacaccc	180
ctnatattct	tctgatacta	aaataatttt	cctagtgtag	tctaaacttt	tttaaaaaga	240
catgtaatcc	gcggagttag	taactcaaaa	cgagtgcata	tnnggaagtat	cgcagccgtt	300
nctggatnaa	attcccagct	tgctngcttg	ctnagccggg	gggcggtnaa	aaaaacatct	360
gcagcccngg	ggnaaaaacc	ttcgcatgtg	tcttacgtgt	ttacgttatt	ttatttccct	420
nnagcaaggc	nggganttgg	ggactcgaaa	tggtacagtt	gggctgggga	tcgcccttgt	480
tacataaaag	ncgtccagaa	gagggacggt	tacaggcngg	ganctccaaa	ggtcagtcct	540
tgccatt						547

&lt;210&gt; 602

&lt;211&gt; 826

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(826)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 602

cggggggnnt	tacgtctctc	tggaacgcttt	tattgtacca	gggcgatccc	agcccaactg	60
taccattcga	gtccctactc	ctgccttget	ctagggaat	aaaataacgt	aaacacgtaa	120
gaacaatgcg	aaagcgtttt	cttccctagg	ctgcagattg	tcttcttcac	cgcccctgct	180
tagctagcta	gctagctggg	aatttaaatcc	agaaacggct	tgcgatacct	cctagatgca	240

ctcgttttga	gttacaaact	ccgcggatta	catgtctttt	taaaaaagtt	tagactacac	300
tagggaaaat	tatttttagta	tcagaagaat	atcaggggggt	gtagtactca	tcagagctna	360
atgagagcgc	tttaaaaatg	ttagtttgtc	ttccgccatt	tctacagaaa	gctgcaattt	420
caggttttca	ncctaatagg	tgatatntaa	gaaaaaaaaa	acaatcgcan	atagcccact	480
gctttttacaa	atcatttttc	tcttctaggt	atagcctgtc	aggtggccta	atgtattttt	540
gacatctcta	ggaattttta	tagaccagaa	atgggtgcc	gagatatgcc	tgactaatc	600
ttaagtgggg	atztatgtat	ttctcaanca	agtgattaaa	gcaaaactag	gcacgaatga	660
aatcaagatc	tttaggccag	aatcatgaa	nanttttana	attattttan	gaatctgtgg	720
cttctcttct	taaaatngaa	aaaaaaattg	tttaaacc	naaggtctga	ataccaagc	780
ncctgaacn	anagaacaan	gccggagcac	cccctcccaa	atcccc		826

&lt;210&gt; 603

&lt;211&gt; 817

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(817)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 603

nnangacttt	tgtggtntta	tacaattntt	ttttctattt	ctatgaagag	aaagccacag	60
agtcctaaaa	taattctaaa	actcatcatg	actttcttgc	ctaaaagatc	ttgatttcaa	120
tcgtgcctag	ttttgcttta	atcaacttgc	tgagaaatac	ataaatcccc	acttaagatt	180
agtgaggca	tatctctggc	acccatttct	ggttctatta	aaattcctag	agatgtcaaa	240
aattacatta	ggccacctga	caggctatac	ctagaagaga	aaaaatgatt	tgtaaaagca	300
gtggggctat	ttgcgattgc	tttttttttt	tcttaaatat	cacctattag	gttgaaaacc	360
tgaaattgca	gctttctgta	gaaatggcgg	aagacaaaact	aacattttta	aagcgctctc	420
atntagctct	gatgagtact	acaccctga	tattcttctg	atactaaaat	aattttccta	480
gtgtagtcta	aactttttta	aaaagacatg	taatccgcgg	agtttgtaac	tcaaaacgag	540
tgcatctagg	aggtatcgca	agccgtttct	ggattaaatt	cccagctagc	ttgcttgctt	600
agcagggggc	ggnaaanaag	acatctgcag	cctagggaag	aaaaccttct	gcattgttct	660
tacgtgttta	cgttatttta	tttcctanaa	caaggcngaa	ttgggactcg	aatggttcag	720
ttgggggtgg	ggatcccctg	gtncataaaa	ngtcanaaag	anggtacagg	cggaaaccca	780
aggtcgtcc	tgcatttana	ctcggaattt	tggtgccc			817

&lt;210&gt; 604

&lt;211&gt; 694

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(694)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 604

cttttcaa	atcattttt	cttctaggta	tancctgtca	ggtggcctaa	tgtaattttt	60
gacatctcta	ngaattttta	tagaaccaga	aatgggtgcc	agagatatgc	ctgcactaat	120
cttaagtggg	gatttatgta	tttctcaagc	aagtgattaa	agcaaaaacta	ggcacgattg	180
aatcaagat	cttttaggca	anaaagtc	gatgagtttt	agaattattt	taggactctg	240
tggtctttct	ttcatagaaa	tagaaaaaaa	aattgtataa	aaccacaaaa	ggtcctgaat	300
agccaaagca	acactganca	aaaagaacan	agcagggaag	caacacacta	ccngaattca	360
aattatacta	ccagggtgta	gtaacaaaaa	cagcattcta	ttggcataaa	atagacacca	420
agaccaatgg	ancagaataa	agaacccac	aaataaatcc	atatatntac	cgccanctga	480
ttatcaataa	cnaacaccaa	gaacatatnt	taagggaacnt	nctattcaat	aantagtgtc	540
ggnaaaaact	gggaaatcca	tatgcagaaa	naatgaaact	agacccctat	ccctcaccat	600

223

acgcaaannt caacttcgga atgggattac aaaacttaag acattccaac ccaagaaact 660  
atnaaancta ctattaagaa aacagatcnc nccc 694

&lt;210&gt; 605

&lt;211&gt; 678

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(678)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 605

taaaaatcta	gactacacta	ggaaattatt	ttantatcag	aagaatatca	ggggtgtagt	60
actcatcana	gctaaatgag	agcgctttta	aaatgttagt	ttgtcttccg	ccattttctac	120
agaaagctgc	aatttcaggt	tttcaaccta	atagggtgata	tttaagaaaa	aaaaaaagca	180
atcgcaaata	gccccactgc	ttttacaaat	cattttttct	cttctaggtta	tagcctgtca	240
ggtggcctaa	tgtaattttt	gacatctcta	ggaattttta	tagaaccaga	aatgggtgcc	300
agagatatgc	ctgcactaat	cttaagtggg	gatttatgta	tttctcaagc	aagtgattaa	360
agcaaaacta	ggcacgattg	aaatcaanat	cttttaggca	agaaagtcac	gatgagtttt	420
anaattattt	taggactctg	tggttttctc	ttcatagaaa	tagaaaaaaa	aaattgtata	480
aaaaccacaa	aaggtcctga	atagcccaaa	gcaacactga	acaaaangaa	caaagcagga	540
agcaacacac	taccggaatt	caattatact	accaaggtgt	antaaccaaa	acagcattct	600
attgggcata	aaatagacca	aagaccagtg	ggaaacagaa	taaagaancc	caaaataaat	660
cctatatatta	cngcccnc					678

&lt;210&gt; 606

&lt;211&gt; 263

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(263)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 606

gtgggggtcng	cancagccaa	ctcagcttcc	tttcgggctt	tgtagcaga	cggatcatcc	60
tctagtccac	tgtgntcaaa	ttccattgtg	tgggggcccnc	tcgctcggc	canagatctg	120
agtgancana	cntgtcccca	ctgaggtgcc	ccacagcngn	ttgtnttcag	cangggctna	180
caactcgacc	ggcagcgan	ggctggcaga	antgngcgcc	tnnctcattc	ctacgcngtn	240
ngccgcagga	aggangacag	gcc				263

&lt;210&gt; 607

&lt;211&gt; 22

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Primer

&lt;400&gt; 607

ccatgtgggt cccggttgct tt

22

&lt;210&gt; 608

&lt;211&gt; 22

&lt;212&gt; DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 608

gataggggtg ctcaggggtt gg

22

<210> 609

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 609

gctggacagg gggcaaaagc tggggcagtg aaccatgtgc

40

<210> 610

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 610

ccttgtccag atagcccagt agctgac

27

<210> 611

<211> 46

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 611

gatagagaaa accgtccagg ccagtattgt gggaggctgg gagtgc

46

<210> 612

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 612

gcacatgggt cactgcccga gcttttgccc cctgtccagc

40

<210> 613

<211> 38

<212> DNA

<213> Artificial Sequence

<220>

&lt;223&gt; Primer

<400> 613  
gccgctcgag ttagaattcg gggttggcca cgatgggtg

38

&lt;210&gt; 614

&lt;211&gt; 53

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Primer

<400> 614  
cggcgggcat atgcatcacc atcaccatca catcataaac ggcgaggact gca

53

&lt;210&gt; 615

&lt;211&gt; 46

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Primer

<400> 615  
gcactccag cctcccacaa tactggcctg gacggttttc tctatc

46

&lt;210&gt; 616

&lt;211&gt; 1350

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<400> 616						60
atgcatcacc	atcaccatca	catcataaac	ggcgaggact	gcagcccgca	ctcgcagccc	120
tggcaggcgg	cactgggtcat	ggaaaacgaa	ttgttctgct	cgggcgtcct	ggtgcatccg	180
cagtgggtgc	tgtagccgc	acactgtttc	cagaactcct	acaccatcgg	gctgggcctg	240
cacagtcttg	aggccgacca	agagccaggg	agccagatgg	tggaggccag	cctctccgta	300
cggcaccag	agtacaacag	acccttgctc	gctaaccgacc	tcatgctcat	caagttggac	360
gaatccgtgt	ccgagtctga	caccatccgg	agcatcagca	ttgcttcgca	gtgccctacc	420
gcggggaaact	cttgccctcg	ttctggctgg	ggtctgctgg	cgaacggcag	aatgcctacc	480
gtgctgcagt	gcgtgaacgt	gtcgggtggtg	tctgaggagg	tctgcagtaa	gctctatgac	540
ccgctgtacc	acccagcat	gttctgcgcc	ggcggagggc	aagaccagaa	ggactcctgc	600
aacgggtgact	ctggggggcc	cctgatctgc	aacgggtact	tgcagggcct	tgtgtctttc	660
ggaaaagccc	cgtgtggcca	agttggcgtg	ccagggtgtct	acaccaacct	ctgcaaattc	720
actgagtga	tagagaaaac	cgtccaggcc	agtattgtgg	gaggctggga	gtgcgagaag	780
cattcccaac	cctggcagg	gcttgtggcc	tctcgtggca	gggcagtctg	cggcggtgtt	840
ctggtgcacc	cccagtgggt	cctcacagct	gccactgca	tcaggaacaa	aagcgtgac	900
ttgctgggtc	ggcacagcct	gtttcatcct	gaagacacag	gccaggtatt	tcaggtcagc	960
cacagcttcc	cacaccgct	ctacgatatg	agcctcctga	agaatcgatt	cctcaggcca	1020
ggtgatgact	ccagccacga	cctcatgctg	ctccgcctgt	cagagcctgc	cgagctcacg	1080
gatgctgtga	aggtcatgga	cctgcccacc	caggagccag	cactggggac	cacctgctac	1140
gcctcaggct	ggggcagcat	tgaaccagag	gagttcttga	cccaaagaa	acttcagtgt	1200
gtggacctcc	atgttatttc	caatgacgtg	tgtgcgcaag	ttcaccctca	gaaggtgacc	1260
aagttcatgc	tgtgtgctgg	acgctggaca	gggggcaaaa	gctggggcag	tgaaccatgt	1320
gccctgcccg	aaaggccttc	cctgtacacc	aaggtggtgc	attaccggaa	gtggatcaag	1350
gacaccatcg	tggccaaccc	cgaattctaa				

&lt;210&gt; 617



<211> 449  
 <212> PRT  
 <213> Homo sapien

<400> 617

Met	His	His	His	His	His	His	Ile	Ile	Asn	Gly	Glu	Asp	Cys	Ser	Pro
1				5					10					15	
His	Ser	Gln	Pro	Trp	Gln	Ala	Ala	Leu	Val	Met	Glu	Asn	Glu	Leu	Phe
			20					25					30		
Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp	Val	Leu	Ser	Ala	Ala	His
		35					40					45			
Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu	Gly	Leu	His	Ser	Leu	Glu
	50					55					60				
Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met	Val	Glu	Ala	Ser	Leu	Ser	Val
65					70					75					80
Arg	His	Pro	Glu	Tyr	Asn	Arg	Pro	Leu	Leu	Ala	Asn	Asp	Leu	Met	Leu
				85					90					95	
Ile	Lys	Leu	Asp	Glu	Ser	Val	Ser	Glu	Ser	Asp	Thr	Ile	Arg	Ser	Ile
			100					105					110		
Ser	Ile	Ala	Ser	Gln	Cys	Pro	Thr	Ala	Gly	Asn	Ser	Cys	Leu	Val	Ser
		115					120					125			
Gly	Trp	Gly	Leu	Leu	Ala	Asn	Gly	Arg	Met	Pro	Thr	Val	Leu	Gln	Cys
	130					135					140				
Val	Asn	Val	Ser	Val	Val	Ser	Glu	Glu	Val	Cys	Ser	Lys	Leu	Tyr	Asp
145					150					155					160
Pro	Leu	Tyr	His	Pro	Ser	Met	Phe	Cys	Ala	Gly	Gly	Gly	Gln	Asp	Gln
				165					170					175	
Lys	Asp	Ser	Cys	Asn	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Ile	Cys	Asn	Gly
			180					185					190		
Tyr	Leu	Gln	Gly	Leu	Val	Ser	Phe	Gly	Lys	Ala	Pro	Cys	Gly	Gln	Val
		195					200					205			
Gly	Val	Pro	Gly	Val	Tyr	Thr	Asn	Leu	Cys	Lys	Phe	Thr	Glu	Trp	Ile
	210					215					220				
Glu	Lys	Thr	Val	Gln	Ala	Ser	Ile	Val	Gly	Gly	Trp	Glu	Cys	Glu	Lys
225					230					235					240
His	Ser	Gln	Pro	Trp	Gln	Val	Leu	Val	Ala	Ser	Arg	Gly	Arg	Ala	Val
				245					250					255	
Cys	Gly	Gly	Val	Leu	Val	His	Pro	Gln	Trp	Val	Leu	Thr	Ala	Ala	His
			260					265					270		
Cys	Ile	Arg	Asn	Lys	Ser	Val	Ile	Leu	Leu	Gly	Arg	His	Ser	Leu	Phe
	275						280					285			
His	Pro	Glu	Asp	Thr	Gly	Gln	Val	Phe	Gln	Val	Ser	His	Ser	Phe	Pro
	290					295					300				
His	Pro	Leu	Tyr	Asp	Met	Ser	Leu	Leu	Lys	Asn	Arg	Phe	Leu	Arg	Pro
305					310					315					320
Gly	Asp	Asp	Ser	Ser	His	Asp	Leu	Met	Leu	Leu	Arg	Leu	Ser	Glu	Pro
				325					330					335	
Ala	Glu	Leu	Thr	Asp	Ala	Val	Lys	Val	Met	Asp	Leu	Pro	Thr	Gln	Glu
			340					345					350		
Pro	Ala	Leu	Gly	Thr	Thr	Cys	Tyr	Ala	Ser	Gly	Trp	Gly	Ser	Ile	Glu
		355					360					365			
Pro	Glu	Glu	Phe	Leu	Thr	Pro	Lys	Lys	Leu	Gln	Cys	Val	Asp	Leu	His
	370					375					380				
Val	Ile	Ser	Asn	Asp	Val	Cys	Ala	Gln	Val	His	Pro	Gln	Lys	Val	Thr
385					390					395					400
Lys	Phe	Met	Leu	Cys	Ala	Gly	Arg	Trp	Thr	Gly	Gly	Lys	Ser	Trp	Gly
				405					410					415	
Ser	Glu	Pro	Cys	Ala	Leu	Pro	Glu	Arg	Pro	S	r	Leu	Tyr	Thr	Lys
															Val

420 425 430  
 Val His Tyr Arg Lys Trp Ile Lys Asp Thr Ile Val Ala Asn Pro Glu  
 435 440 445  
 Phe

<210> 618  
 <211> 3923  
 <212> DNA  
 <213> Homo sapien

<400> 618  
 acagaagaaa tagcaagtgc cgagaagctg gcatcagaaa aacagagggg agatttgtgt 60  
 ggctgcagcc gagggagacc aggaagatct gcatggtggg aaggacctga tgatacagag 120  
 gaattacaac acatatactt agtgtttcaa tgaacaccaa gataaataag tgaagagcta 180  
 gtccgctgtg agtctcctca gtgacacagg gctggatcac catcgacggc actttctgag 240  
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&lt;210&gt; 619

&lt;211&gt; 3674

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 619

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&lt;210&gt; 620

&lt;211&gt; 2051

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(2051)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 620

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&lt;210&gt; 621

&lt;211&gt; 2841

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(2841)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 621

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&lt;210&gt; 622

&lt;211&gt; 3228

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(3228)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 622

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&lt;211&gt; 4894

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 623

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&lt;210&gt; 624

&lt;211&gt; 2904

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 624

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&lt;210&gt; 625

&lt;211&gt; 4034

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 625

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&lt;400&gt; 626

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&lt;210&gt; 627

&lt;211&gt; 123

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 627

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Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val
      20                                25                        30

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Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys
      35                                40                        45

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Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu Thr Gly
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Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala Ser Leu
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Tyr His Arg Glu Lys Gln Val Leu Ile Gly Gln Trp Val Glu Ser Gly
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<210> 628

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Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val  
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Glu Glu Lys Phe Met Thr Met Val Leu Gly Glu Ser Leu His Pro Pro  
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Ser Phe Leu Phe Gln Ile His Ala Thr Trp His Val Gly Gln Glu Tyr  
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Leu Cys Pro Gly Ser Cys Leu Glu Gly Glu Val Val Cys Trp Glu Gly  
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Ile Ala Gly Gln Glu Gly Asp Pro Gly Leu Arg Gly His Thr Lys Arg  
 100 105 110

Lys Lys Arg Ile Pro Arg Thr Tyr Pro Ser His Leu Trp Ile Pro Gly  
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Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala  
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Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp  
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 Cys Phe Thr Pro Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro  
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 Asp His Cys Arg Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu  
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 Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala  
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 Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg  
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 Pro Ile Cys Ile His Gly Phe Ser Trp Val Trp Asn Ile Ser Ala Cys  
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Ala Pro Val  
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 <211> 2983  
 <212> DNA  
 <213> Homo sapiens

<400> 630  
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&lt;210&gt; 631

&lt;211&gt; 3064

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 631

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&lt;210&gt; 632

&lt;211&gt; 684

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 632

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Asn Gln Asp Asn Ala Val Ser His His Thr Trp Glu Phe Gln Thr Ser
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Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu
      35              40              45

Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
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Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
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Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
      85              90              95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile
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Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
      115             120             125

Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu
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Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu
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Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys
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Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys
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Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp
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Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys
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Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly

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 Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser  
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 Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val  
 290                      295                      300  
 Asp Thr Tyr Val Asn Glu Asn Gly Lys Lys Ile Thr Ser Met Thr His  
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 Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg  
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 Pro Asp Leu Pro Lys Gly Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr  
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 Pro Gln Glu Arg Ser Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu  
 355                      360                      365  
 Thr Ala Ile Arg Lys Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe  
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 Val Phe Ser Glu Val Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met  
 385                      390                      395                      400  
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 405                      410                      415  
 Ile Gly Lys Asn Ile Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg  
 420                      425                      430  
 Asp Ile Thr Tyr Glu Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg  
 435                      440                      445  
 Gln Val Met Asp His Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His  
 450                      455                      460  
 Arg Arg Pro Val Lys Glu Asn Phe Leu His Met Ser Val Gln Ser Asp  
 465                      470                      475                      480  
 Asp Val Leu Leu Gly Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg  
 485                      490                      495  
 Lys Thr Ala Ala Leu Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu  
 500                      505                      510  
 Gln Leu Tyr Thr Gly Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys  
 515                      520                      525  
 Thr Ser Gln Ile Gln Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp  
 530                      535                      540

Ser Lys Thr Tyr Ile Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val  
 545 550 555 560  
 Ile Arg Gly Phe Ile Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met  
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 Ala Ser Glu Val Phe Thr Ser Phe Gln Tyr Pro Glu Phe Ser Ile Glu  
 580 585 590  
 Leu Pro Asn Thr Gly Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile  
 595 600 605  
 Phe Lys Asn Thr Leu Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu  
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 Glu Ser Leu Gly Ile Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val  
 625 630 635 640  
 Gln Pro Gly Glu Thr Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys  
 645 650 655  
 Thr Gly Pro Lys Lys Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys  
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 Glu Ile Asn Ala Gln Lys Ile Val Leu Ile Thr Lys  
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&lt;210&gt; 633

&lt;211&gt; 679

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 633

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 Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu  
 35 40 45  
 Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr  
 50 55 60  
 Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro  
 65 70 75 80  
 Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu  
 85 90 95  
 Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile  
 100 105 110  
 Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys  
 115 120 125

S r Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu  
130 135 140

~~Asp Met Val Phe Met Pro Asn Glu Asn Glu Arg Lys Glu Thr Ile Leu~~  
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Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys  
165 170 175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys  
180 185 190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp  
195 200 205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys  
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Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly  
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Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr  
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Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala  
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Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser  
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Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val  
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Asp Thr Tyr Val Asn Glu Asn Gly Glu Lys Ile Thr Ser Met Thr His  
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Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg  
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Pro Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr Pro Gln Glu Arg Ser  
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Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu Thr Ala Ile Arg Lys  
355 360 365

Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe Val Phe Ser Glu Val  
370 375 380

Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met Val Asn Gly Gln Glu  
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Glu Leu His Val Il Ser Met Glu Thr Thr Ser Ile Gly Lys Asn Ile  
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Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg Asp Ile Thr Tyr Glu  
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Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg Gln Val Met Asp His

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Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg Lys Thr Ala Ala Leu		
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Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu Gln Leu Tyr Thr Gly		
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Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys Thr Ser Gln Ile Gln		
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Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp Ser Lys Thr Tyr Ile		
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Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val Ile Arg Gly Phe Ile		
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Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met Ala Ser Glu Val Phe		
	565	570
Thr Ser Asn Gln Tyr Pro Glu Phe Ser Ile Glu Leu Pro Asn Thr Gly		
	580	585
Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile Phe Lys Asn Thr Leu		
	595	600
Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu Glu Ser Leu Gly Ile		
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Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val Gln Pro Gly Glu Thr		
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Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys Thr Gly Pro Lys Lys		
	645	650
Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys Glu Ile Asn Ala Gln		
	660	665
Lys Ile Val Leu Ile Thr Lys		
675		

&lt;210&gt; 634

&lt;211&gt; 5668

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 634

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&lt;211&gt; 1095

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 635

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Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg  
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Glu Ile Ala Asn Lys Ile Lys  
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&lt;211&gt; 1095

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(1095)

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&lt;400&gt; 637

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Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
      65                                70                                75                                80

```

```

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
      85                                90                                95

```

```

Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser

```

255

100					105					110					
Cys	Asp	Thr	Asp	Ala	Glu	Ile	Leu	Tyr	Glu	Leu	Leu	Thr	Gln	His	Trp
	115						120					125			
His	Leu	Lys	Thr	Pro	Asn	Leu	Val	Ile	Ser	Val	Thr	Gly	Gly	Ala	Lys
	130					135					140				
Asn	Phe	Ala	Leu	Lys	Pro	Arg	Met	Arg	Lys	Ile	Phe	Ser	Arg	Leu	Ile
145					150					155					160
Tyr	Ile	Ala	Gln	Ser	Lys	Gly	Ala	Trp	Ile	Leu	Thr	Gly	Gly	Thr	His
				165					170					175	
Tyr	Gly	Leu	Met	Lys	Tyr	Ile	Gly	Glu	Val	Val	Arg	Asp	Asn	Thr	Ile
		180						185					190		
Ser	Arg	Ser	Ser	Glu	Glu	Asn	Ile	Val	Ala	Ile	Gly	Ile	Ala	Ala	Trp
		195					200					205			
Gly	Met	Val	Ser	Asn	Arg	Asp	Thr	Leu	Ile	Arg	Asn	Cys	Asp	Ala	Glu
	210					215					220				
Gly	Tyr	Phe	Leu	Ala	Gln	Tyr	Leu	Met	Asp	Asp	Phe	Thr	Arg	Asp	Pro
225					230					235					240
Leu	Tyr	Ile	Leu	Asp	Asn	Asn	His	Thr	His	Leu	Leu	Leu	Val	Asp	Asn
			245						250					255	
Gly	Cys	His	Gly	His	Pro	Thr	Val	Glu	Ala	Lys	Leu	Arg	Asn	Gln	Leu
			260					265					270		
Glu	Lys	Tyr	Ile	Ser	Glu	Arg	Thr	Ile	Gln	Asp	Ser	Asn	Tyr	Gly	Gly
		275					280					285			
Lys	Ile	Pro	Ile	Val	Cys	Phe	Ala	Gln	Gly	Gly	Gly	Lys	Glu	Thr	Leu
	290					295					300				
Lys	Ala	Ile	Asn	Thr	Ser	Ile	Lys	Asn	Lys	Ile	Pro	Cys	Val	Val	Val
305					310					315					320
Glu	Gly	Ser	Gly	Gln	Ile	Ala	Asp	Val	Ile	Ala	Ser	Leu	Val	Glu	Val
			325						330					335	
Glu	Asp	Ala	Leu	Thr	Ser	Ser	Ala	Val	Lys	Glu	Lys	Leu	Val	Arg	Phe
		340						345					350		
Leu	Pro	Arg	Thr	Val	Ser	Arg	Leu	Pro	Glu	Glu	Glu	Thr	Glu	Ser	Trp
		355					360					365			
Ile	Lys	Trp	Leu	Lys	Glu	Ile	Leu	Glu	Cys	Ser	His	Leu	Leu	Thr	Val
	370					375					380				
Ile	Lys	Met	Glu	Glu	Ala	Gly	Asp	Glu	Ile	Val	Ser	Asn	Ala	Ile	Ser
385					390					395					400
Tyr	Ala	Leu	Tyr	Lys	Ala	Phe	Ser	Thr	Ser	Glu	Gln	Asp	Lys	Asp	Asn
				405					410					415	

Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu  
 420 425 430  
 Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp  
 435 440 445  
 Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe  
 450 455 460  
 Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr  
 465 470 475 480  
 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val  
 485 490 495  
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu  
 500 505 510  
 Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys  
 515 520 525  
 Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val  
 530 535 540  
 Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile  
 545 550 555 560  
 Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg  
 565 570 575  
 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu  
 580 585 590  
 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu  
 595 600 605  
 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr  
 610 615 620  
 Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu  
 625 630 635 640  
 Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp  
 645 650 655  
 Gln His Phe Ile Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln  
 660 665 670  
 Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu  
 675 680 685  
 Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg  
 690 695 700  
 Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala  
 705 710 715 720

Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr  
 725 730 735  
 Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His  
 740 745 750  
 Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val  
 755 760 765  
 Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly Val Asn Tyr  
 770 775 780  
 Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe  
 785 790 795 800  
 Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu  
 805 810 815  
 Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu  
 820 825 830  
 Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile  
 835 840 845  
 Ile Met Leu Gln Arg Met Leu Ile Asp Val Phe Phe Phe Leu Phe Leu  
 850 855 860  
 Phe Ala Xaa Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu  
 865 870 875 880  
 Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr  
 885 890 895  
 Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly  
 900 905 910  
 Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys  
 915 920 925  
 Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu  
 930 935 940  
 Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile  
 945 950 955 960  
 Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr  
 965 970 975  
 Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu  
 980 985 990  
 Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val  
 995 1000 1005  
 Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys  
 1010 1015 1020  
 Lys Glu Lys Asn M t Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp



1025                      1030                      1035                      1040  
 Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val  
                          1045                      1050                      1055  
 Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg  
                          1060                      1065                      1070  
 Phe Arg Gln Leu Asp Thr Lys Leu Asn Asp Leu Lys Gly Leu Leu Lys  
                          1075                      1080                      1085  
 Glu Ile Ala Asn Lys Ile Lys  
                          1090                      1095

<210> 638  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

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    5                      10                      15

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 <212> DNA  
 <213> Homo sapiens

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<210> 640  
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<400> 640  
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<210> 641  
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<400> 641  
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<210> 642  
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<212> DNA  
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45

<210> 644  
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<212> DNA  
<213> Homo sapiens

<400> 644  
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42

<210> 645  
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<212> DNA  
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<400> 645  
ctgtcagccg cacactgttt ccagaactcc tacaccatcg ggctg

45

<210> 646  
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<212> DNA  
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45

<210> 647  
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<212> DNA  
<213> Homo sapiens

<400> 647  
tcgggcgtcc tgggtgcatcc gcagtgggtg ctgtcagccg cacac

45

<210> 648  
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<212> DNA  
<213> Homo sapiens

<400> 648  
aacgaattgt tctgctcggg cgtcctggtg catccgcagt ggggtg

45

<210> 649  
<211> 45  
<212> DNA  
<213> Homo sapiens

<400> 649  
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45

<210> 650  
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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 650

tcgcagccct ggcaggcggc actggtcattg gaaaacgaat tgttctgctc g 51

&lt;210&gt; 651

&lt;211&gt; 45

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 651

atcagcattg cttcgcagtg ccctaccgag gggaactctt gcctc 45

&lt;210&gt; 652

&lt;211&gt; 45

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 652

tccgtgtccg agtctgacac catccggagc atcagcattg cttcg 45

&lt;210&gt; 653

&lt;211&gt; 45

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 653

atcaagttgg acgaatccgt gtccgagtct gacaccatcc ggagc 45

&lt;210&gt; 654

&lt;211&gt; 45

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 654

aacgacctca tgctcatcaa gttggacgaa tccgtgtccg agtct 45

&lt;210&gt; 655

&lt;211&gt; 45

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 655

agacccttgc tcgctaacga cctcatgctc atcaagttgg acgaa 45

&lt;210&gt; 656

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 656

Glu Pro Gly Ser Gln Met Val Glu Ala Ser Leu Ser Val Arg His  
5 10 15

&lt;210&gt; 657

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 657

Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala Ser Leu  
5 10 15

&lt;210&gt; 658

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 658

Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met  
5 10 15

&lt;210&gt; 659

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 659

Tyr Thr Ile Gly Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu  
5 10 15

&lt;210&gt; 660

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 660

Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu  
5 10

&lt;210&gt; 661

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 661

Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu  
5 10 15

&lt;210&gt; 662

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 662

His Pro Gln Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser  
5 10 15

<210> 663  
<211> 15  
<212> PRT  
<213> Homo sapiens

<400> 663  
Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Ala His  
5 10 15

<210> 664  
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<213> Homo sapiens

<400> 664  
Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val  
5 10 15

<210> 665  
<211> 15  
<212> PRT  
<213> Homo sapiens

<400> 665  
Ala Leu Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val  
5 10 15

<210> 666  
<211> 17  
<212> PRT  
<213> Homo sapiens

<400> 666  
Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu Phe Cys  
5 10 15

Ser

<210> 667  
<211> 15  
<212> PRT  
<213> Homo sapiens

<400> 667  
Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu  
5 10 15

<210> 668  
<211> 15  
<212> PRT  
<213> Homo sapiens

263

&lt;400&gt; 668

Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser  
5 10 15

&lt;210&gt; 669

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 669

Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser  
5 10 15

&lt;210&gt; 670

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 670

Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser  
5 10 15

&lt;210&gt; 671

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 671

Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu  
5 10 15

&lt;210&gt; 672

&lt;211&gt; 35

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 672

ggaccagcat atgaggaaca gaaggaatga cactc

35

&lt;210&gt; 673

&lt;211&gt; 29

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 673

ccgctcgagt ccacccaag cttcacagg

29

<210> 674  
 <211> 1959  
 <212> DNA  
 <213> Homo sapiens

<400> 674

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aagaaacgag aatgtgtctt ctttaccaaa gattccaagg ccacggagaa tgtgtgcaag 180
tgtggctatg cccagagcca gcacatggaa ggcaeccaga tcaaccaaag tgagaaatgg 240
aactacaaga aacacaccaa ggaatttcct accgacgcct ttggggatat tcagtttgag 300
acactgggga agaaagggaa gtatatacgt ctgtcctgcg acacggacgc ggaaatcctt 360
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tacatcgcgc agtccaaagg tgcttggatt ctacgggag gcacccatta tggcctgatg 540
aagtacatcg gggagggtgt gagagataac accatcagca ggagttcaga ggagaatatt 600
gtggccattg gcatagcagc ttggggcctg gtctccaacc gggacaccct catcagggaat 660
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ctgtatatcc tggacaacaa ccacacacat ttgtgtctcg tggacaatgg ctgtcatgga 780
catcccactg tcgaagcaaa gctccggaat cagctagaga agtatatctc tgagcgcaact 840
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gcttgggggtg gactcgagca ccaccaccac caccactga 1959

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<210> 675  
 <211> 652  
 <212> PRT  
 <213> Homo sapiens

<400> 675

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Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
      5                                10                                15

Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
      20                                25                                30

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
      35                                40                                45

Thr Lys Asp S r Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
      50                                55                                60

```

265

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp  
 65 70 75 80  
 Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp  
 85 90 95  
 Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser  
 100 105 110  
 Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp  
 115 120 125  
 His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys  
 130 135 140  
 Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile  
 145 150 155 160  
 Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His  
 165 170 175  
 Tyr Gly Leu Met Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile  
 180 185 190  
 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp  
 195 200 205  
 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu  
 210 215 220  
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro  
 225 230 235 240  
 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn  
 245 250 255  
 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu  
 260 265 270  
 Glu Lys Tyr Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly  
 275 280 285  
 Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu  
 290 295 300  
 Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val  
 305 310 315 320  
 Glu Gly Ser Gly Gln Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val  
 325 330 335  
 Glu Asp Ala Leu Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe  
 340 345 350  
 Leu Pro Arg Thr Val Ser Arg Leu Pro Glu Glu Glu Thr Glu Ser Trp  
 355 360 365  
 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val



370	375	380
Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser		
385	390	395 400
Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn		
	405	410 415
Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu		
	420	425 430
Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp		
	435	440 445
Leu Glu Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe		
	450	455 460
Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr		
	465	470 475 480
His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val		
	485	490 495
Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu		
	500	505 510
Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys		
	515	520 525
Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val		
	530	535 540
Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile		
	545	550 555 560
Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg		
	565	570 575
Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu		
	580	585 590
Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu		
	595	600 605
Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr		
	610	615 620
Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu		
	625	630 635 640
Ala Trp Gly Gly Leu Glu His His His His His His		
	645	650

&lt;210&gt; 676

&lt;211&gt; 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 676

```

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1      5      10      15
Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
20      25      30
Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
35      40      45
Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
50      55      60
Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65      70      75      80
Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
85      90      95
Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
100     105     110
Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
115     120     125
Gly Pro Pro Ala
130

```

&lt;210&gt; 677

&lt;211&gt; 36

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 677

ggggaattca tgatccggga gaaatttgcc cactgc

36

&lt;210&gt; 678

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 678

gggctcgagt caggagtttg agaccagcct ggc

33

&lt;210&gt; 679

&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 679

```

atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60
cagggttcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120

```

```

accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgacagag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
gcgcttaacg ggcatcatcc cggtgacgtc atctcggtga cctggcaaac caagtcgggc 360
ggcacgcgta cagggaacgt gacattggcc gagggacccc cggccgaatt catgatccgg 420
gagaaatttg cccactgcac cgtgctaacc attgcacaca gattgaacac cattattgac 480
agcgacaaga taatggtttt agattcagga agactgaaag aatatgatga gccgtatgtt 540
ttgctgcaaa ataaagagag cctattttac aagatgggtc aacaactggg caaggcagaa 600
gccgctgccc tcactgaaac agcaaaacag agatgggggt tcaccatgtt ggccaggctg 660
gtctcaaact cctga 675

```

&lt;210&gt; 680

&lt;211&gt; 291

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 680

```

atggggatcc gggagaaaatt tgcccactgc accgtgctaa ccattgcaca cagattgaac 60
accattattg acagcgacaa gataatggtt ttagattcag gaagactgaa agaatatgat 120
gagccgtatg ttttgctgca aaataaagag agcctathtt acaagatggt gcaacaactg 180
ggcaaggcag aagccgctgc cctcactgaa acagcaaaac agagatgggg ttccaccatg 240
ttggccaggc tgggtctcaaa ctccctcgag caccaccacc accaccactg a 291

```

&lt;210&gt; 681

&lt;211&gt; 1074

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 681

```

atgtcagcca ttgagagggt gtcagaggca atcgtcagca tccgaagaat ccagaccttt 60
ttgctacttg atgagatatc acagcgcaac cgtcagctgc cgtcagatgg taaaaagatg 120
gtgcatgtgc aggattttac tgctttttgg gataaggcat cagagacccc aactctacaa 180
ggcctttcct ttactgtcag acctggcgaa ttgttagctg tggtcggccc cgtgggagca 240
gggaagtcat cactgttaag tgccgtgctc ggggaattgg ccccaagtca cgggctggtc 300
agcgtgcatg gaagaattgc ctatgtgtct cagcagccct ggggtgtctc gggaactctg 360
aggagtaata ttttattttg gaagaaatac gaaaaggaaac gatatgaaaa agtcataaag 420
gcttgtgtct tgaaaaagga ttacagctg ttggaggatg gtgatctgac tgtgatagga 480
gatcggggaa ccacgctgag tggagggcag aaagcacggg taaaccttgc aagagcagtg 540
tatcaagatg ctgacatcta tctcctggac gatcctctca gtgcagtaga tgcggaagt 600
agcagacact tggtcgaact gtgtatttgt caaattttgc atgagaagat cacaatttta 660
gtgactcatc agttgcagta cctcaaagct gcaagtcaga ttctgatatt gaaagatggt 720
aaaatggtgc agaaggggac ttacactgag ttcttaaaat ctggtataga ttttggtccc 780
cttttaaaaga aggataatga ggaaagtga caacctccag ttccagggaac tcccacacta 840
aggaatcgta ccttctcaga gtcttcggtt tgggtctcaac aatcttctag accctccttg 900
aaagatggtg ctctggagag ccaagataca gagaatgtcc cagttacact atcagaggag 960
aaccgttctg aaggaaaagt tggttttcag gcctataaga attacttcag agctgggtgct 1020
cactggattg tcttcatttt ccttattctc gagcaccacc accaccacca ctga 1074

```

&lt;210&gt; 682

&lt;211&gt; 224

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 682

```

Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
      5                                10                    15

```

```

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala

```

	20		25		30										
Ile	Ala	Gly	Gln	Ile	Lys	Leu	Pro	Thr	Val	His	Ile	Gly	Pro	Thr	Ala
		35					40					45			
Phe	Leu	Gly	Leu	Gly	Val	Val	Asp	Asn	Asn	Gly	Asn	Gly	Ala	Arg	Val
	50					55					60				
Gln	Arg	Val	Val	Gly	Ser	Ala	Pro	Ala	Ala	Ser	Leu	Gly	Ile	Ser	Thr
	65				70					75					80
Gly	Asp	Val	Ile	Thr	Ala	Val	Asp	Gly	Ala	Pro	Ile	Asn	Ser	Ala	Thr
				85					90					95	
Ala	Met	Ala	Asp	Ala	Leu	Asn	Gly	His	His	Pro	Gly	Asp	Val	Ile	Ser
			100					105					110		
Val	Thr	Trp	Gln	Thr	Lys	Ser	Gly	Gly	Thr	Arg	Thr	Gly	Asn	Val	Thr
		115					120					125			
Leu	Ala	Glu	Gly	Pro	Pro	Ala	Glu	Phe	Met	Ile	Arg	Glu	Lys	Phe	Ala
	130					135					140				
His	Cys	Thr	Val	Leu	Thr	Ile	Ala	His	Arg	Leu	Asn	Thr	Ile	Ile	Asp
145					150					155					160
Ser	Asp	Lys	Ile	Met	Val	Leu	Asp	Ser	Gly	Arg	Leu	Lys	Glu	Tyr	Asp
				165					170					175	
Glu	Pro	Tyr	Val	Leu	Leu	Gln	Asn	Lys	Glu	Ser	Leu	Phe	Tyr	Lys	Met
			180					185					190		
Val	Gln	Gln	Leu	Gly	Lys	Ala	Glu	Ala	Ala	Ala	Leu	Thr	Glu	Thr	Ala
	195						200					205			
Lys	Gln	Arg	Trp	Gly	Phe	Thr	Met	Leu	Ala	Arg	Leu	Val	Ser	Asn	Ser
	210					215					220				

&lt;210&gt; 683

&lt;211&gt; 357

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 683

Met	Ser	Ala	Ile	Glu	Arg	Val	Ser	Glu	Ala	Ile	Val	Ser	Ile	Arg	Arg
				5				10						15	

Ile	Gln	Thr	Phe	Leu	Leu	Leu	Asp	Glu	Ile	Ser	Gln	Arg	Asn	Arg	Gln
		20						25					30		

Leu	Pro	Ser	Asp	Gly	Lys	Lys	Met	Val	His	Val	Gln	Asp	Phe	Thr	Ala
		35					40					45			

Phe	Trp	Asp	Lys	Ala	Ser	Glu	Thr	Pro	Thr	Leu	Gln	Gly	Leu	Ser	Phe
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

270

50		55		60
Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly Ala				
65		70		75
				80
Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro Ser				
	85		90	95
His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln Gln				
	100		105	110
Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly Lys				
	115		120	125
Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala Leu				
	130		135	140
Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile Gly				
	145		150	155
Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn Leu				
	165		170	175
Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp Pro				
	180		185	190
Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu Cys				
	195		200	205
Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val Thr His Gln				
	210		215	220
Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp Gly				
	225		230	235
Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe Leu Lys Ser Gly Ile				
	245		250	255
Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn Glu Glu Ser Glu Gln Pro				
	260		265	270
Pro Val Pro Gly Thr Pro Thr Leu Arg Asn Arg Thr Phe Ser Glu Ser				
	275		280	285
Ser Val Trp Ser Gln Gln Ser Ser Arg Pro Ser Leu Lys Asp Gly Ala				
	290		295	300
Leu Glu Ser Gln Asp Thr Glu Asn Val Pro Val Thr Leu Ser Glu Glu				
	305		310	315
Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr Phe				
	325		330	335
Arg Ala Gly Ala His Trp Ile Val Phe Ile Phe Leu Ile Leu Glu His				
	340		345	350
His His His His His				
	355			

271

<210> 684  
<211> 96  
<212> PRT  
<213> Homo sapiens

<400> 684  
Met Gly Ile Arg Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala  
5 10 15  
His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp  
20 25 30  
Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn  
35 40 45  
Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu  
50 55 60  
Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Arg Trp Gly Phe Thr Met  
65 70 75 80  
Leu Ala Arg Leu Val Ser Asn Ser Leu Glu His His His His His His  
85 90 95

<210> 685  
<211> 35  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 685  
cgcccatggg gatccgggag aaatttgccc actgc

35

<210> 686  
<211> 35  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 686  
cgcctcgagg gagtttgaga ccagcctggc caaca

35

<210> 687  
<211> 38  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 687  
gcatggacca tatgtcagcc attgagaggg tgtcagag

38

<210> 688  
<211> 34  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 688  
ccgctcgaga ataaggaaaa tgaagacaat ccag

34

<210> 689  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 689  
gttgaattca tgcacgggcc ccagggtg

27

<210> 690  
<211> 30  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 690  
cccctcgagt cactatgggc tgcctcttga

30

<210> 691  
<211> 915  
<212> DNA  
<213> Homo sapiens

<400> 691  
atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60  
cagggattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120  
accgttcata tggggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180  
ggcgacagag tccaacgcgt ggtcgggagc gtcggggcg caagtctcgg catctccacc 240  
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300  
gcgcttaacg ggcacatcc cggtgacgtc atctcgggtga cctggcaaac caagtcgggc 360  
ggcacgcgta cagggaaacgt gacattggcc gagggacccc cggccgaatt catgcacggg 420  
ccccagggtg tggcacgctg ctccgagtgt gcttgtcctg ccttggctgc cacctctgcg 480  
gggggtgcgtc tggagggggt ggaccggcca ccaaccttac ccagtcaagg aagtggatgg 540  
ccatgttccc acagcctgag tggctgccac ctgatggctg atggagcaaa ggccttagga 600  
aaagcagatg gcccttggcc ctaccttttt gttagaagaa ctgatgttcc atgtcctgca 660  
gcgagtgagg ttggtggctg tgcccccagc tcttggcgcg ccctcgcaga ggtgactggt 720

<213> Homo sapiens

Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu  
5 10 15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala  
20 25 30

Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala  
35 40 45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val  
50 55 60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr  
65 70 75 80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr  
85 90 95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser  
100 105 110

Val	Thr	Trp	Gln	Thr	Lys	Ser	Gly	Gly	Thr	Arg	Thr	Gly	Asn	Val	Thr
		115					120					125			

Leu Ala Glu Gly Pro Pro Ala Glu Phe Met His Gly Pro Gln Val Leu  
130 135 140

Ala Arg Cys Ser Glu Cys Ala Cys Pro Ala Leu Ala Ala Thr Ser Ala  
145 150 155 160

Gly Val Arg Leu Glu Gly Val Asp Arg Pro Pro Thr Leu Pro Ser Gln  
165 170 175

Gly Ser Gly Trp Pro Cys Ser His Ser Leu Ser Gly Cys His Leu Met  
180 185 190

Ala Asp Gly Ala Lys Ala Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr  
195 200 205

Leu Phe Val Arg Arg Thr Asp Val Pro Cys Pro Ala Ala Ser Glu Val  
210 215 220

Gly Gly Cys Ala Pro Ser Ser Trp Arg Ala Leu Ala Glu Val Thr Gly  
225 230 235 240

Cys Ser Leu Gly Pro Leu Gly Leu Ala Gln His Ala Gln Ala Ser Val  
245 250 255



274

Leu Leu Leu Cys Tyr Lys Trp Ser His Ile Gly Glu Thr Ser Ser His  
 260 265 270

Leu Arg Ser Lys Val Tyr Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu  
 275 280 285

Lys Gly Leu Met Ser Leu Trp Ala Ser Trp Leu Ser Arg Gly Arg Pro  
 290 295 300

&lt;210&gt; 693

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 693

cgaagtcacg tggaggccag cctc

24

&lt;210&gt; 694

&lt;211&gt; 29

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 694

cctgaccgaa ttcattaact ggcctggac

29

&lt;210&gt; 695

&lt;211&gt; 166

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(166)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 695

Met Gly His His His His His Val Glu Ala Ser Leu Ser Val Arg  
 1 5 10 15  
 His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile  
 20 25 30  
 Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser  
 35 40 45  
 Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser Gly  
 50 55 60  
 Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys Val  
 65 70 75 80  
 Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp Pro



<211> 241  
 <212> PRT  
 <213> Homo sapiens

<400> 699

Met	Gln	His	His	His	His	His	His	Leu	Arg	Val	Pro	Glu	Pro	Arg	Pro
1				5					10					15	
Gly	Glu	Ala	Lys	Ala	Glu	Gly	Ala	Ala	Pro	Pro	Thr	Pro	Ser	Lys	Pro
			20					25					30		
Leu	Thr	Ser	Phe	Leu	Ile	Gln	Asp	Ile	Leu	Arg	Asp	Gly	Ala	Gln	Arg
		35					40					45			
Gln	Gly	Gly	Arg	Thr	Ser	Ser	Gln	Arg	Gln	Arg	Asp	Pro	Glu	Pro	Glu
	50					55					60				
Pro	Glu	Pro	Glu	Pro	Glu	Gly	Gly	Arg	Ser	Arg	Ala	Gly	Ala	Gln	Asn
65					70					75				80	
Asp	Gln	Leu	Ser	Thr	Gly	Pro	Arg	Ala	Ala	Pro	Glu	Glu	Ala	Glu	Thr
				85					90					95	
Leu	Ala	Glu	Thr	Glu	Pro	Glu	Arg	His	Leu	Gly	Ser	Tyr	Leu	Leu	Asp
			100					105					110		
Ser	Glu	Asn	Thr	Ser	Gly	Ala	Leu	Pro	Arg	Leu	Pro	Gln	Thr	Pro	Lys
		115					120					125			
Gln	Pro	Gln	Lys	Arg	Ser	Arg	Ala	Ala	Phe	Ser	His	Thr	Gln	Val	Ile
	130						135					140			
Glu	Leu	Glu	Arg	Lys	Phe	Ser	His	Gln	Lys	Tyr	Leu	Ser	Ala	Pro	Glu
145					150					155				160	
Arg	Ala	His	Leu	Ala	Lys	Asn	Leu	Lys	Leu	Thr	Glu	Thr	Gln	Val	Lys
				165					170					175	
Ile	Trp	Phe	Gln	Asn	Arg	Arg	Tyr	Lys	Thr	Lys	Arg	Lys	Gln	Leu	Ser
			180					185					190		
Ser	Glu	Leu	Gly	Asp	Leu	Glu	Lys	His	Ser	Ser	Leu	Pro	Ala	Leu	Lys
	195						200					205			
Glu	Glu	Ala	Phe	Ser	Arg	Ala	Ser	Leu	Val	Ser	Val	Tyr	Asn	Ser	Tyr
	210					215					220				
Pro	Tyr	Tyr	Pro	Tyr	Leu	Tyr	Cys	Val	Gly	Ser	Trp	Ser	Pro	Ala	Phe
225					230					235					240
Trp															

<210> 700  
 <211> 729  
 <212> DNA  
 <213> Homo sapiens

<400> 700

atgcagcatc	accaccatca	ccacctcagg	gttcgggagc	cgcgcccg	ggaggcgaaa	60
gcggaggggg	ccgcgccgcc	gaccccgctc	aagccgctca	cgctcttct	catccaggac	120
atcctgcggg	acggcgcgca	gcggcaaggc	ggccgcacga	gcagccagag	acagcgcgac	180
ccggagccgg	agccagagcc	agagccagag	ggaggacgca	gccgcgccgg	ggcgagaaac	240
gaccagctga	gcaccggggc	ccgcgcccg	ccggatgagg	ccgagacgct	ggcagagacc	300
gagccagaaa	ggcacttggg	gtcttatctg	ttggactctg	aaaacacttc	aggcgccctt	360
ccaaggcttc	cccaaacc	taagcagccg	cagaagcgct	cccagagctg	cttctccac	420
actcaggtga	tgcagttgga	gaggaagttc	agccatcaga	agtagctgtc	ggcccctgaa	480
cgggcccacc	tggccaagaa	cctcaagctc	acggagaccc	aagtgaagat	atggttccag	540
aacagacgct	ataagactaa	gcgaaagcag	ctctcctcgg	agctgggaga	cttgagagaag	600
cactcctttt	tgcggccct	gaaagaggag	gccttctccc	gggcctccct	ggtctccgtg	660
tataacagct	atccttacta	cccatacctg	cactgcgtgg	gcagctggag	cccagctttt	720
tggtaatga						729

277

<210> 701  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 701  
 ctactaagcg ctggagtggag ggatcag

27

<210> 702  
 <211> 33  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 702  
 catcgagaat tcactactct ctgactagat gtc

33

<210> 703  
 <211> 161  
 <212> PRT  
 <213> Homo sapiens

<400> 703  
 Met Gln His His His His His His Ala Gly Val Arg Asp Gln Gly Gln  
 1 5 10 15  
 Gly Ala Arg Trp Pro His Thr Gly Lys Arg Gly Pro Leu Leu Gln Gly  
 20 25 30  
 Leu Thr Trp Ala Thr Gly Gly His Cys Phe Ser Ser Glu Glu Ser Gly  
 35 40 45  
 Ala Val Asp Gly Ala Gly Gln Lys Lys Asp Arg Ala Trp Leu Arg Cys  
 50 55 60  
 Pro Glu Ala Val Ala Gly Phe Pro Leu Gly Ser Asp Cys Arg Glu Gly  
 65 70 75 80  
 Gly Arg Gln Gly Cys Gly Gly Ser Asp Asp Glu Asp Asp Leu Gly Val  
 85 90 95  
 Ala Pro Gly Leu Ala Pro Ala Trp Ala Leu Thr Gln Pro Pro Ser Gln  
 100 105 110  
 Ser Pro Gly Pro Gln Ser Leu Pro Ser Thr Pro Ser Ser Ile Trp Pro  
 115 120 125  
 Gln Trp Val Ile Leu Ile Thr Glu Leu Thr Ile Pro Ser Pro Ala His  
 130 135 140  
 Gly Pro Pro Trp Leu Pro Asn Ala Leu Glu Arg Gly His Leu Val Arg  
 145 150 155 160  
 Glu

<210> 704  
 <211> 489  
 <212> DNA  
 <213> Homo sapiens

<400> 704  
 atgcagcatc accaccatca ccacgctgga gtgagggatc aggggagagg cgcgagatgg 60  
 cctcacacag ggaagagagg gcccctcctg cagggcctca cctggggccac aggaggacac 120  
 tgcttttccct ctgaggagtc aggagctgtg gatggtgctg gacagaagaa ggacagggcc 180  
 tggctcaggt gtccagaggc tgcgctggc ttccctttgg gatcagactg cagggagggg 240  
 gggcggcagg gttgtggggg gagtgcgat gaggatgacc tgggggtggc tccaggcctt 300  
 gccctgcct gggccctcac ccagcctccc tcacagtctc ctggccctca gtctctcccc 360  
 tccactccat cctccatctg gcctcagtg gtcattctga tcaactgaact gaccataccc 420  
 agccctgccc acggccctcc atggctcccc aatgcctgg agaggggaca tctagtcaga 480  
 gagtagtga 489

<210> 705  
 <211> 132  
 <212> PRT  
 <213> Homo sapiens

<400> 705  
 Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe  
 1 5 10 15  
 Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser  
 20 25 30  
 Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly  
 35 40 45  
 Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val  
 50 55 60  
 Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val  
 65 70 75 80  
 Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala  
 85 90 95  
 Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp  
 100 105 110  
 Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu  
 115 120 125  
 Gly Pro Pro Ala  
 130

<210> 706  
 <211> 31  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 706  
 ggggaattca tcacctatgt gccgcctctg c

31

<210> 707  
 <211> 40  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

&lt;400&gt; 707

gggctcgagt cactcgccca cgaaatccgt gtaaaacagc

40

&lt;210&gt; 708

&lt;211&gt; 1203

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 708

```

atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60
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&lt;210&gt; 709

&lt;211&gt; 400

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 709

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Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala
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      35              40              45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
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Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
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Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser

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280

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<212> DNA  
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Met Val Leu

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<213> Homo sapiens

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 Thr Lys Tyr Lys Lys Phe Pro His Trp Leu Asp Lys Trp Met Leu Thr  
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325

330

335

Ser Gln Leu

&lt;210&gt; 737

&lt;211&gt; 2172

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 737

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&lt;211&gt; 2455

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 738

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 739

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```

&lt;210&gt; 740

&lt;211&gt; 62

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 740

```

Met Thr His Ser Ser Ala Trp Leu Glu Arg Pro Gln Glu Thr Tyr Asn
          5                      10                      15

```

```

His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln
          20                      25                      30

```

```

Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu
          35                      40                      45

```

```

Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala
          50                      55                      60

```

&lt;210&gt; 741

&lt;211&gt; 135

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 741

```

Met Val Glu Gly Glu Gly Glu Ala Arg His Val Leu His Gly Gly Arg
          5                      10                      15

```



290

Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg  
20 25 30

Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu  
35 40 45

Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu  
50 55 60

Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala  
65 70 75 80

Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly  
85 90 95

Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro  
100 105 110

Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile  
115 120 125

Leu Leu Asn Tyr Gln Val Ser  
130 135

&lt;210&gt; 742

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 742

Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln  
5 10 15

Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His  
20 25 30

Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro  
35 40 45

Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln  
50 55 60

Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu  
65 70 75

&lt;210&gt; 743

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 743

Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly  
5 10 15

Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser  
20 25 30

Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser  
           35                          40                          45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe  
       50                          55                          60

<210> 744  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 744  
 Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
                           5                          10                          15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
                           20                          25                          30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
                           35                          40                          45  
 Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
                           50                          55                          60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
       65                          70                          75

<210> 745  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 745  
 Met Val Lys Ser Arg Phe Thr Lys Asn Thr Lys Ile Thr Gln Ala Trp  
                           5                          10                          15

Trp Arg Ala Pro Val Ile Pro Gly Thr Arg Glu Ala Glu Gly Gly Glu  
                           20                          25                          30

Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly  
                           35                          40                          45

Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp  
                           50                          55                          60

Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys  
       65                          70                          75

<210> 746  
 <211> 80  
 <212> PRT  
 <213> Homo sapiens

<400> 746  
 Met Leu Leu His Ser Ser Leu Val Asn Arg Ala Arg Leu Cys Leu Lys

292

5 10 15  
 Asn Lys Gln Ile Asn Lys Gln Thr Asn Lys Thr Glu Arg Phe Cys Cys  
 20 25 30  
 Asn Val Gln Gly Ala Ile Cys Ser Phe Lys Lys Ile Ile Phe Gly Gln  
 35 40 45  
 Ala Gln Trp Leu Thr Pro Val Ile Pro Ala Leu Trp Glu Ala Lys Val  
 50 55 60  
 Gly Gly Ser Phe Glu Val Arg Ser Leu Arg Ser Ala Trp Pro Thr Trp  
 65 70 75 80

<210> 747  
 <211> 72  
 <212> PRT  
 <213> Homo sapiens

<400> 747  
 Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro His Asn Pro  
 5 10 15  
 Ile Thr Ser His Gln Val Ser Ser Asp Thr Trp Asp Trp Val Gly Thr  
 20 25 30  
 Gln Ser Gln Thr Val Ser Asp Ala Ala Gly Ala Gly Asp Thr Glu Thr  
 35 40 45  
 Thr Gln Thr Trp Cys Leu Cys His Ser Ser Gly Leu Cys Leu Ser Pro  
 50 55 60  
 Gly Pro Pro Ser Pro Ser Met Val  
 65 70

<210> 748  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<400> 748  
 Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln  
 5 10 15  
 Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His  
 20 25 30  
 Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro  
 35 40 45  
 Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln  
 50 55 60  
 Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu  
 65 70 75

<400> 749																
Met	Leu	Val	His	Ile	Tyr	Ser	Cys	Cys	Gly	Met	Val	Tyr	Arg	Phe	Gly	
				5					10					15		
Gln	Met	Ser	Asp	Asn	Pro	Phe	Tyr	Ile	Leu	Ala	Ser	Leu	Gly	Ser	Ser	
			20					25					30			
Ser	Cys	Arg	Asn	Gly	Leu	Ala	Ser	Lys	Trp	Arg	Gln	Ala	Asp	Pro	Ser	
		35					40					45				
Asp	Gly	Tyr	Met	Glu	Pro	Cys	Phe	Gln	Leu	Leu	Phe					
	50					55					60					

```
<210> 750
<211> 76
<212> PRT
<213> Homo sapiens
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<400> 750  
Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
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Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Gln Leu Gly Ser Arg  
20 25 30  
Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
35 40 45  
Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
50 55 60  
Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
65 70 75

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<210> 751
<211> 2479
<212> DNA
<213> Homo sapiens
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<400> 751						
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agaaagcact	gtgcatcacc	ttgacctggg	ggaccttcct	cgtgggagct	gcgctggcgg	360
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```

&lt;210&gt; 752

&lt;211&gt; 492

&lt;212&gt; PRT

&lt;213&gt; Homo .sapiens

&lt;400&gt; 752

Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu  
5 10 15

Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val  
20 25 30

Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro  
35 40 45

Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val  
50 55 60

Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys  
65 70 75 80

Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Ph Leu Val  
85 90 95

Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys

100					105					110					
Cys	Ser	Asn	Ser	Gly	Ile	Glu	Cys	Asp	Ser	Ser	Gly	Thr	Cys	Ile	Asn
		115					120					125			
Pro	Ser	Asn	Trp	Cys	Asp	Gly	Val	Ser	His	Cys	Pro	Gly	Gly	Glu	Asp
		130				135					140				
Glu	Asn	Arg	Cys	Val	Arg	Leu	Tyr	Gly	Pro	Asn	Phe	Ile	Leu	Gln	Met
145					150					155					160
Tyr	Ser	Ser	Gln	Arg	Lys	Ser	Trp	His	Pro	Val	Cys	Gln	Asp	Asp	Trp
				165					170					175	
Asn	Glu	Asn	Tyr	Gly	Arg	Ala	Ala	Cys	Arg	Asp	Met	Gly	Tyr	Lys	Asn
			180					185					190		
Asn	Phe	Tyr	Ser	Ser	Gln	Gly	Ile	Val	Asp	Asp	Ser	Gly	Ser	Thr	Ser
		195					200					205			
Phe	Met	Lys	Leu	Asn	Thr	Ser	Ala	Gly	Asn	Val	Asp	Ile	Tyr	Lys	Lys
	210					215					220				
Leu	Tyr	His	Ser	Asp	Ala	Cys	Ser	Ser	Lys	Ala	Val	Val	Ser	Leu	Arg
225					230					235					240
Cys	Leu	Ala	Cys	Gly	Val	Asn	Leu	Asn	Ser	Ser	Arg	Gln	Ser	Arg	Ile
				245					250					255	
Val	Gly	Gly	Glu	Ser	Ala	Leu	Pro	Gly	Ala	Trp	Pro	Trp	Gln	Val	Ser
			260					265					270		
Leu	His	Val	Gln	Asn	Val	His	Val	Cys	Gly	Gly	Ser	Ile	Ile	Thr	Pro
		275					280					285			
Glu	Trp	Ile	Val	Thr	Ala	Ala	His	Cys	Val	Glu	Lys	Pro	Leu	Asn	Asn
	290					295					300				
Pro	Trp	His	Trp	Thr	Ala	Phe	Ala	Gly	Ile	Leu	Arg	Gln	Ser	Phe	Met
305					310					315					320
Phe	Tyr	Gly	Ala	Gly	Tyr	Gln	Val	Gln	Lys	Val	Ile	Ser	His	Pro	Asn
				325					330					335	
Tyr	Asp	Ser	Lys	Thr	Lys	Asn	Asn	Asp	Ile	Ala	Leu	Met	Lys	Leu	Gln
			340					345					350		
Lys	Pro	Leu	Thr	Phe	Asn	Asp	Leu	Val	Lys	Pro	Val	Cys	Leu	Pro	Asn
		355					360					365			
Pro	Gly	Met	Met	Leu	Gln	Pro	Glu	Gln	Leu	Cys	Trp	Ile	Ser	Gly	Trp
	370					375					380				
Gly	Ala	Thr	Glu	Glu	Lys	Gly	Lys	Thr	Ser	Glu	Val	Leu	Asn	Ala	Ala
385					390					395					400
Lys	Val	Leu	Leu	Ile	Glu	Thr	Gln	Arg	Cys	Asn	Ser	Arg	Tyr	Val	Tyr
				405					410					415	

Asp Asn Leu Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly  
420 425 430

Asn Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser  
435 440 445

Asn Asn Asn Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly  
450 455 460

Cys Ala Lys Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe  
465 470 475 480

Thr Asp Trp Ile Tyr Arg Gln Met Lys Ala Asn Gly  
485 490

<210> 753

<211> 683

<212> DNA

<213> Homo sapiens

<400> 753

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gggcggcctg cagggacatg ggctataaga ataattttta ctctagccaa ggaatagtgg 660
atgacagcgg atccaccagc ttt 683
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<210> 754

<211> 209

<212> PRT

<213> Homo sapiens

<400> 754

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Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
20 25 30
Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
35 40 45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
50 55 60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
65 70 75 80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
85 90 95
```

297

Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys  
                   100                  105                  110  
 Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn  
                   115                  120                  125  
 Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp  
                   130                  135                  140  
 Glu Asn Arg Cys Val Arg Leu Tyr Gly Pro Asn Phe Ile Leu Gln Met  
 145                  150                  155                  160  
 Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp  
                   165                  170                  175  
 Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn  
                   180                  185                  190  
 Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser  
                   195                  200                  205  
 Phe

<210> 755  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 755  
 Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr  
   1                  5                  10                  15  
 Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg  
                   20                  25

<210> 756  
 <211> 35  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

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 ggatccgccc ccaccatgtc actttctagc ctgct

35

<210> 757  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 757  
 gtcgactcag ctggaccaca gccgcag

27

<210> 758  
 <211> 34  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer



<400> 758  
ggatccgccc ccaccatggg ctgcaggctg ctct

34

<210> 759  
<211> 27  
<212> DNA  
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<220>  
<223> PCR primer

<400> 759  
gtcgactcag aaatcctttc tcttgac

27

<210> 760  
<211> 936  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...()  
<223> n = A,T,C or G

<400> 760  
atgggctgca ggctgntctg ctgtgcggtt ctctgtctcc tgggagcggg ccccatggaa 60  
acgggagtta cgcagacacc aagacacctg gtcatgggaa tgacaaataa gaagtctttg 120  
aaatgtgaac aacatctggg tcataacgct atgtattggg acaagcaaag tgctaagaag 180  
ccaactggagc tcatgtttgt ctacagtctt gaagaacggg ttgaaaacaa cagtgtgcca 240  
agtcgcttct cacctgaatg ccccaacagc tctcacttat tccttcacct acacaccctg 300  
cagccagaag actcggccct gtatctctgc gccagcagcc aagaccggac aagcagctcc 360  
tacgagcagt acttcgggcc gggcaccagg ctacagggtc cagaggacct gaaaaacgtg 420  
ttcccacccg aggtcgctgt gtttgagcca tcagaagcag agatctccca caccacaaaag 480  
gccacactgg tgtgcctggc cacaggcttc taccgagacc acgtggagct gagctggtgg 540  
gtgaatggga aggaggtgca cagtggggtc agcacagacc cgcagcccct caaggagcag 600  
cccgcctca atgactccag atactgcctg agcagccgcc tgagggtctc ggccaccttc 660  
tggcagaacc cccgcaacca cttccgctgt caagtccagt tctacgggct ctcgagaaat 720  
gacgagtgga cccaggatag ggccaaacct gtcaccacaga tcgtcagcgc cgaggcctgg 780  
ggtagagcag actgtggctt cacctccgag tcttaccagc aaggggtcct gtctgccacc 840  
atcctctatg agatcttgct agggaaggcc accttgtatg ccgtgctggt cagtgccctc 900  
gtgctgatgg ccatgggtcaa gagaaaggat ttctga 936

<210> 761  
<211> 834  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...()  
<223> n = A,T,C or G

<400> 761  
atgtcacttt ctagcctgct naagggtggtc acagcttcac tgtgggctagg acctggcatt 60  
gccagaaga taactcaaac ccaaccagga atgttcgtgc aggaaaagga ggctgtgact 120  
ctggactgca catatgacac cagtgatcaa agttatggtc tcttctggta caagcagccc 180

```

agcagtgggg aaatgatttt ttttatttat caggggtctt atgacgagca aaatgcaaca 240
gaaggtcgct actcattgaa tttccagaag gcaagaaaaat cgcaccaacct tgtcatctcc 300
gcttcacaac tgggggactc agcaatgtat ttctgtgcaa tgagagaggg cgcgggagga 360
ggaaacaaaac tcacctttgg gacaggcact cagctaaaaag tggaactcaa tatccagaac 420
cctgaccctg ccgtgtacca gctgagagac tctaaatcca gtgacaagtc tgtctgccta 480
ttcaccgatt ttgattctca aacaaatgtg tcacaaagta aggattctga tgtgtatatc 540
acagacaaaa ctgtgctaga catgaggtct atggacttca agagcaacag tgctgtggcc 600
tggagcaaca aatctgactt tgcattgtgca aacgccttca acaacagcat tattccagaa 660
gacaccttct tccccagccc agaaagttcc tgtgatgtca agctggtcga gaaaagcttt 720
gaaacagata cgaacctaaa ctttcaaaac ctgtcagtga ttgggttccg aatcctcttc 780
ctgaaagtgg ccgggtttta tctgctcatg acgtgcggc tggtgtccag ctga 834

```

&lt;210&gt; 762

&lt;211&gt; 311

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; variant

&lt;222&gt; (1)...(311)

&lt;223&gt; Xaa = Any amino acid

&lt;400&gt; 762

```

Met Gly Cys Arg Leu Xaa Cys Cys Ala Val Leu Cys Leu Leu Gly Ala
      5                      10                      15

```

```

Val Pro Met Glu Thr Gly Val Thr Gln Thr Pro Arg His Leu Val Met
      20                      25                      30

```

```

Gly Met Thr Asn Lys Lys Ser Leu Lys Cys Glu Gln His Leu Gly His
      35                      40                      45

```

```

Asn Ala Met Tyr Trp Tyr Lys Gln Ser Ala Lys Lys Pro Leu Glu Leu
      50                      55                      60

```

```

Met Phe Val Tyr Ser Leu Glu Glu Arg Val Glu Asn Asn Ser Val Pro
      65                      70                      75                      80

```

```

Ser Arg Phe Ser Pro Glu Cys Pro Asn Ser Ser His Leu Phe Leu His
      85                      90                      95

```

```

Leu His Thr Leu Gln Pro Glu Asp Ser Ala Leu Tyr Leu Cys Ala Ser
      100                     105                     110

```

```

Ser Gln Asp Arg Thr Ser Ser Ser Tyr Glu Gln Tyr Phe Gly Pro Gly
      115                     120                     125

```

```

Thr Arg Leu Thr Val Thr Glu Asp Leu Lys Asn Val Phe Pro Pro Glu
      130                     135                     140

```

```

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
      145                     150                     155                     160

```

```

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu
      165                     170                     175

```

```

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
      180                     185                     190

```

300

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr  
 195 200 205  
 Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro  
 210 215 220  
 Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn  
 225 230 235 240  
 Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser  
 245 250 255  
 Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr  
 260 265 270  
 Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly  
 275 280 285  
 Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala  
 290 295 300  
 Met Val Lys Arg Lys Asp Phe  
 305 310

&lt;210&gt; 763

&lt;211&gt; 277

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 763

Met Ser Leu Ser Ser Leu Leu Lys Val Val Thr Ala Ser Leu Trp Leu  
 5 10 15  
 Gly Pro Gly Ile Ala Gln Lys Ile Thr Gln Thr Gln Pro Gly Met Phe  
 20 25 30  
 Val Gln Glu Lys Glu Ala Val Thr Leu Asp Cys Thr Tyr Asp Thr Ser  
 35 40 45  
 Asp Gln Ser Tyr Gly Leu Phe Trp Tyr Lys Gln Pro Ser Ser Gly Glu  
 50 55 60  
 Met Ile Phe Leu Ile Tyr Gln Gly Ser Tyr Asp Glu Gln Asn Ala Thr  
 65 70 75 80  
 Glu Gly Arg Tyr Ser Leu Asn Phe Gln Lys Ala Arg Lys Ser Ala Asn  
 85 90 95  
 Leu Val Ile Ser Ala Ser Gln Leu Gly Asp Ser Ala Met Tyr Phe Cys  
 100 105 110  
 Ala Met Arg Glu Gly Ala Gly Gly Gly Asn Lys Leu Thr Phe Gly Thr  
 115 120 125  
 Gly Thr Gln Leu Lys Val Glu Leu Asn Ile Gln Asn Pro Asp Pro Ala  
 130 135 140

Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu  
145 150 155 160

Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser  
165 170 175

Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp  
180 185 190

Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala  
195 200 205

Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe  
210 215 220

Pro Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe  
225 230 235 240

Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe  
245 250 255

Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu  
260 265 270

Arg Leu Trp Ser Ser  
275

<210> 764

<211> 1536

<212> DNA

<213> Homo sapiens

<400> 764

atgtacaacc	tggttgcgtgc	ctacgacaga	catgggggacc	acctgcagcc	cctggacctc	60
gtgcccgaatc	accagggtct	cacccctttc	aagctggctg	gagtggagg	taacactgtg	120
atgtttcagc	acctgatgca	gaagcgggaag	cacacccagt	ggacgtatgg	accactgacc	180
tcgactctct	atgacctcac	agagatcgac	tcctcagggg	atgagcagtc	cctgctggaa	240
cttatcatca	ccaccaagaa	gcgggaggct	cgccagatcc	tggaaccagac	gccggtgaag	300
gagctggtga	gcctcaagt	gaagcgggtac	gggcggccgt	acttctgcat	gctgggtgcc	360
atatatctgc	tgtacatcat	ctgcttcacc	atgtgctgca	tctaccgccc	cctcaagccc	420
aggaccaata	accgcacgag	cccccgggac	aacaccctct	tacagcagaa	gctacttcag	480
gaagcctaca	tgacccttaa	ggacgatata	cggctggctg	gggagctgg	gactgtcatt	540
ggggctatat	tcatacctgct	ggtagagggt	ccagacatct	tcagaatggg	ggtcactcgc	600
ttctttggag	agaccatcct	tgggggccca	ttccatgtcc	tcatacatcac	ctatgccttc	660
atggtgctgg	tgaccatggg	gatgcggctc	atcagtgcca	gcggggagg	ggtacccatg	720
tcctttgcac	tcgtgctggg	ctggtgcaac	gtcatgtact	tcgcccagg	attccagatg	780
ctaggccct	tcacatcat	gattcagaag	atgatttttg	gcgacctgat	gcgattctgc	840
tggtgatgg	ctgtggtcat	cctgggcttt	gcttcagcct	tctatatcat	cttcagaca	900
gaggaccccg	aggagctagg	ccacttctac	gactacccca	tgccctgtt	cagcaccttc	960
gagctgttcc	ttacatcat	cgatggccca	gccaaactaca	acgtggacct	gcccttcagt	1020
tacagcatca	cctatgctgc	ctttgccatc	atcgccacac	tgctcatgct	caacctctc	1080
attgccatga	tgggcgacac	tactggcga	gtggcccatg	agcgggatga	gctgtggagg	1140
gccagattg	tggccaccac	ggtgatgctg	gagcggaagc	tgccctcgctg	cctgtggcct	1200
cgctccggga	tctgcggacg	ggagtatggc	ctgggagacc	gctggttcct	gcgggtggaa	1260
gacaggcaag	atctcaaccg	gcagcggatc	caacgctacg	cacaggcctt	ccacaccccg	1320
ggctctgagg	atttggaaca	agactcagtg	gaaaaactag	agctgggctg	tcccttcagc	1380

```
<210> 765
<211> 1533
<212> DNA
<213> Homo sapiens
```

<b>&lt;400&gt; 765</b>						
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gtgccaatc	accagggtct	cacccctttc	aagctggctg	gagtggaggg	taacactgtg	120
atgtttcagc	acctgatgca	gaagcggaag	cacacccagt	ggacgtatgg	accactgacc	180
togactctct	atgacctcac	agagatcgac	tcctcagggg	atgagcagtc	cctgctggaa	240
cttatcatca	ccaccaagaa	gcgggagggt	cgccagatcc	tggaccagac	gccggtgaag	300
gagctgggtga	gcctcaagtg	gaagcggtag	ggcgggccgt	actttcgcat	gctgggtgcc	360
atatactctgc	tgtacatcat	ctgcttcacc	atgtgtcgca	ctaccgccc	cctcaagccc	420
aggaccaata	accgcacgag	ccccgggac	aacacctct	tacagcagaa	gctacttcag	480
gaagcctaca	tgacccctaa	ggacgatatc	cggctggctg	gggagctggt	gactgtcatt	540
ggggctatca	tcatcctgct	ggtagagggt	ccagacatct	tcagaatggg	ggtcactcgc	600
ttctttggac	agaccatcct	tgggggcccc	ttccatgtcc	tcatcatcac	ctatgccttc	660
atggtgctgg	tgaccatggt	gatgcggtc	atcagtgcca	gcggggaggt	ggtacccatg	720
tcctttgcac	tcgtgctggg	ctggtgcaac	gtcatgtact	tcgcccagag	attccagatg	780
ctaggccccct	tcaccatcat	gattcagaag	atgatttttg	gcgacctgat	gcgattctgc	840
tggtctgatgg	ctgtggctcat	cttgggcttt	gcttcagcct	tctatatcat	cttcagaca	900
gaggaccccg	aggagctagg	ccacttctac	gactacccc	tgcctctgtt	cagcaccttc	960
gagctgttcc	ttaccatcat	cgatggcccc	gccaactaca	acgtggacct	gcccttcatg	1020
tacagcatca	cctatgctgc	ctttgccatc	atcgccacac	tgtcatgct	caacctcctc	1080
attgccatga	tgggcgacac	tcaactggcg	gtggcccatg	agcgggatga	gctgtggagg	1140
gccagattg	tggccaccac	ggtgatgctg	gagcggaagc	tgcctcgctg	cctgtggcct	1200
cgctccggga	tctgcggacg	ggagtatggc	ctgggagacc	gctggttcct	gcgggtggaa	1260
gacagtgcaag	atctcaaccg	gcagcggatc	caacgctacg	cacaggcctt	ccacaccccg	1320
ggctctgagg	atttggacaa	agactcagtg	gaaaaactag	agctgggctg	tcccttcagc	1380
ccccacctgt	cccttcctat	gccctcagtg	tctcgaagta	cctccgcgag	cagtgccaat	1440
tgggaaaggc	ttcggcaagg	gcacctgagg	agagacctgc	gtgggataat	caacaggggt	1500
ctggaggacg	gggagagctg	ggaatatcag	atc			1533

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<210> 766
<211> 511
<212> PRT
<213> Homo sapiens
```

BNSDOCID: <WO 0151633A2 I >

Leu Ile Ile Thr Thr Lys Lys Arg Glu Ala Arg Gln Ile Leu Asp Gln  
                                     85                                    90                                    95  
 Thr Pro Val Lys Glu Leu Val Ser Leu Lys Trp Lys Arg Tyr Gly Arg  
                                     100                                    105                                    110  
 Pro Tyr Phe Cys Met Leu Gly Ala Ile Tyr Leu Leu Tyr Ile Ile Cys  
                                     115                                    120                                    125  
 Phe Thr Met Cys Cys Ile Tyr Arg Pro Leu Lys Pro Arg Thr Asn Asn  
                                     130                                    135                                    140  
 Arg Thr Ser Pro Arg Asp Asn Thr Leu Leu Gln Gln Lys Leu Leu Gln  
 145                                    150                                    155                                    160  
 Glu Ala Tyr Met Thr Pro Lys Asp Asp Ile Arg Leu Val Gly Glu Leu  
                                     165                                    170                                    175  
 Val Thr Val Ile Gly Ala Ile Ile Ile Leu Leu Val Glu Val Pro Asp  
                                     180                                    185                                    190  
 Ile Phe Arg Met Gly Val Thr Arg Phe Phe Gly Gln Thr Ile Leu Gly  
                                     195                                    200                                    205  
 Gly Pro Phe His Val Leu Ile Ile Thr Tyr Ala Phe Met Val Leu Val  
                                     210                                    215                                    220  
 Thr Met Val Met Arg Leu Ile Ser Ala Ser Gly Glu Val Val Pro Met  
 225                                    230                                    235                                    240  
 Ser Phe Ala Leu Val Leu Gly Trp Cys Asn Val Met Tyr Phe Ala Arg  
                                     245                                    250                                    255  
 Gly Phe Gln Met Leu Gly Pro Phe Thr Ile Met Ile Gln Lys Met Ile  
                                     260                                    265                                    270

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Phe Gly Asp Leu Met Arg Phe Cys Trp Leu Met Ala Val Val Ile Leu  
                                     275                                    280                                    285  
 Gly Phe Ala Ser Ala Phe Tyr Ile Ile Phe Gln Thr Glu Asp Pro Glu  
                                     290                                    295                                    300  
 Glu Leu Gly His Phe Tyr Asp Tyr Pro Met Ala Leu Phe Ser Thr Phe  
 305                                    310                                    315                                    320  
 Glu Leu Phe Leu Thr Ile Ile Asp Gly Pro Ala Asn Tyr Asn Val Asp  
                                     325                                    330                                    335  
 Leu Pro Phe Met Tyr Ser Ile Thr Tyr Ala Ala Phe Ala Ile Ile Ala  
                                     340                                    345                                    350  
 Thr Leu Leu Met Leu Asn Leu Leu Ile Ala Met Met Gly Asp Thr His  
                                     355                                    360                                    365  
 Trp Arg Val Ala His Glu Arg Asp Glu Leu Trp Arg Ala Gln Ile Val  
                                     370                                    375                                    380  
 Ala Thr Thr Val Met Leu Glu Arg Lys Leu Pro Arg Cys Leu Trp Pro

385                      390                      395                      400  
 Arg Ser Gly Ile Cys Gly Arg Glu Tyr Gly Leu Gly Asp Arg Trp Phe  
                          405                      410                      415  
 Leu Arg Val Glu Asp Arg Gln Asp Leu Asn Arg Gln Arg Ile Gln Arg  
                          420                      425                      430  
 Tyr Ala Gln Ala Phe His Thr Arg Gly Ser Glu Asp Leu Asp Lys Asp  
                          435                      440                      445  
 Ser Val Glu Lys Leu Glu Leu Gly Cys Pro Phe Ser Pro His Leu Ser  
                          450                      455                      460  
 Leu Pro Met Pro Ser Val Ser Arg Ser Thr Ser Arg Ser Ser Ala Asn  
                          465                      470                      475                      480  
 Trp Glu Arg Leu Arg Gln Gly Thr Leu Arg Arg Asp Leu Arg Gly Ile  
                          485                      490                      495  
 Ile Asn Arg Gly Leu Glu Asp Gly Glu Ser Trp Glu Tyr Gln Ile  
                          500                      505                      510

&lt;210&gt; 767

&lt;211&gt; 134

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 767

Met Tyr Asn Leu Leu Leu Ser Tyr Asp Arg His Gly Asp His Leu Gln  
    5                      10                      15  
 Pro Leu Asp Leu Val Pro Asn His Gln Gly Leu Thr Pro Phe Lys Leu  
    20                      25                      30  
 Ala Gly Val Glu Gly Asn Thr Val Met Phe Gln His Leu Met Gln Lys  
    35                      40                      45  
 Arg Lys His Thr Gln Trp Thr Tyr Gly Pro Leu Thr Ser Thr Leu Tyr  
    50                      55                      60  
 Asp Leu Thr Glu Ile Asp Ser Ser Gly Asp Glu Gln Ser Leu Leu Glu  
    65                      70                      75                      80  
 Leu Ile Ile Thr Thr Lys Lys Arg Glu Ala Arg Gln Ile Leu Asp Gln  
    85                      90                      95  
 Thr Pro Val Lys Glu Leu Val Ser Leu Lys Trp Lys Arg Tyr Gly Arg  
    100                      105                      110  
 Pro Tyr Phe Cys Met Leu Gly Ala Ile Tyr Leu Leu Tyr Ile Ile Cys  
    115                      120                      125  
 Phe Thr Met Cys Cys Ile  
    130

305

<210> 768  
 <211> 55  
 <212> PRT  
 <213> Homo sapiens

<400> 768  
 Ala Tyr Arg Pro Leu Lys Pro Arg Thr Asn Asn Arg Thr Ser Pro Arg  
                   5                  10                  15  
 Asp Asn Thr Leu Leu Gln Gln Lys Leu Leu Gln Glu Ala Tyr Met Thr  
           20                  25                  30  
 Pro Lys Asp Asp Ile Arg Leu Val Gly Glu Leu Val Thr Val Ile Gly  
           35                  40                  45  
 Ala Ile Ile Ile Leu Leu Val  
       50                  55

<210> 769  
 <211> 39  
 <212> PRT  
 <213> Homo sapiens

<400> 769  
 Glu Val Pro Asp Ile Phe Arg Met Gly Val Thr Arg Phe Phe Gly Gln  
                   5                  10                  15  
 Thr Ile Leu Gly Gly Pro Phe His Val Leu Ile Ile Thr Tyr Ala Phe  
           20                  25                  30  
 Met Val Leu Val Thr Met Val  
       35

<210> 770  
 <211> 19  
 <212> PRT  
 <213> Homo sapiens

<400> 770  
 Met Arg Leu Ile Ser Ala Ser Gly Glu Val Val Pro Met Ser Phe Ala  
                   5                  10                  15  
 Leu Val Leu

<210> 771  
 <211> 52  
 <212> PRT  
 <213> Homo sapiens

<400> 771  
 Gly Trp Cys Asn Val Met Tyr Phe Ala Arg Gly Phe Gln Met Leu Gly  
                   5                  10                  15  
 Pro Phe Thr Ile Met Ile Gln Lys Met Ile Phe Gly Asp Leu Met Arg



```
<210> 772
<211> 213
<212> PRT
<213> Homo sapiens
```

Gln Thr Glu Asp Pro Glu Glu Leu Gly His Phe Tyr Asp Tyr Pro Met  
5 10 15

Ala Leu Phe Ser Thr Phe Glu Leu Phe Leu Thr Ile Ile Asp Gly Pro  
20 25 30

Ala Asn Tyr Asn Val Asp Leu Pro Phe Met Tyr Ser Ile Thr Tyr Ala  
35 40 45

Ala Phe Ala Ile Ile Ala Thr Leu Leu Met Leu Asn Leu Leu Ile Ala  
50 55 60

Met Met Gly Asp Thr His Trp Arg Val Ala His Glu Arg Asp Glu Leu  
65 70 75 80

Trp Arg Ala Gln Ile Val Ala Thr Thr Val Met Leu Glu Arg Lys Leu  
85 90 95

Pro Arg Cys Leu Trp Pro Arg Ser Gly Ile Cys Gly Arg Glu Tyr Gly  
100 105 110

Leu Gly Asp Arg Trp Phe Leu Arg Val Glu Asp Arg Gln Asp Leu Asn  
115 120 125

Arg Gln Arg Ile Gln Arg Tyr Ala Gln Ala Phe His Thr Arg Gly Ser  
130 135 140

Glu Asp Leu Asp Lys Asp Ser Val Glu Lys Leu Glu Leu Gly Cys Pro  
145 150 155 160

Phe Ser Pro His Leu Ser Leu Pro Met Pro Ser Val Ser Arg Ser Thr  
165 170 175

Ser Arg Ser Ser Ala Asn Trp Glu Arg Leu Arg Gln Gly Thr Leu Arg  
180 185 190

Arg Asp Leu Arg Gly Ile Ile Asn Arg Gly Leu Glu Asp Gly Glu Ser  
195 200 205

Trp Glu Tyr Gln Ile  
210

<210> 773  
<211> 1302  
<212> DNA  
<213> Homo sapiens

<400> 773

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tcacagttca	gcttcttcat	gatgggtgat	cccaatggca	atgaatccag	tgctacatac	120
ttcatcctaa	taggcctccc	tggtttagaa	gaggctcagt	tctgggtggc	cttcccattg	180
tgctccctct	accttattgc	tgtgctaggt	aacttgacaa	tcactctacat	tgtgoggact	240
gagcacagcc	tgcattgagcc	catgtatata	tttctttgca	tgctttcagg	battgacatc	300
ctcatctcca	cctcatccat	gcccataatg	ctggccatct	tctgggtcaa	ttccactacc	360
atccagtgtg	atgcttgtct	gctacagatg	tttgccatcc	actccttate	tggeatggaa	420
tccacagtgc	tgtgggcat	ggcttttgac	cgctatgtgg	ccatctgtca	cccactgcgc	480
catgccacag	tacttacgtt	gcctcgtgtc	accaaattg	gtgtggctgc	tgtggtgcgg	540
ggggctgcac	tgatggcacc	ccttcctgtc	ttcatcaagc	agctgccctt	ctgccgctcc	600
aatatccttt	cccattccta	ctgcctacac	caagatgtca	tgaagctggc	ctgtgatgat	660
atccgggtca	atgtcgtcta	tggccttate	gtcatcatct	ccgccattgg	cctggactca	720
cttctcatct	ccttctcata	tctgcttatt	cttaagactg	tgttgggctt	gacacgtgaa	780
gccagggcca	aggcatttgg	cacttgcgct	tctcatgtgt	gtgctgtgtt	catattctat	840
gtaccctttca	tggattgtc	catgggtgat	cgctttagca	agcggcgtga	ctctccgctg	900
cccgctcatct	tggccaatat	ctatctgctg	gttccctcctg	tgtcaaoccc	aattgtctat	960
ggagtgaaga	caaaggagat	tcgacagcgc	atccttcgac	ttttccatgt	ggccacacac	1020
gcttcagagc	cctaggtgtc	agtgatcaaa	cttcttttcc	attcagagtc	ctctgattca	1080
gatttttaatg	ttaacatttt	ggaagacagt	attcagaaaa	aaaatttcc	taataaaaaat	1140
acaactcaga	tccttcaaat	atgaaactgg	ttgggggaatc	tccatttttt	caatattatt	1200
ttcttctttg	ttttcttgct	acatataatt	attaataccc	tgactaggtt	gtgggttgag	1260
ggttattact	tttcatttta	ccatgcagtc	caaactctaaa	ct		1302

<210> 774  
<211> 2061  
<212> DNA  
<213> Homo sapiens

<400> 774

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gtgtcagtga	tcaaacttct	tttccattca	gagtcctctg	attcagattt	taatgttaac	120
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&lt;211&gt; 957

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 775

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&lt;211&gt; 954

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 776

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Ile Tyr Ile Val Arg Thr Glu His Ser Leu His Glu Pro Met Tyr Ile  
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Phe Leu Cys Met Leu Ser Gly Ile Asp Ile Leu Ile Ser Thr Ser Ser  
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Met Pro Lys Met Leu Ala Ile Phe Trp Phe Asn Ser Thr Thr Ile Gln  
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Phe Asp Ala Cys Leu Leu Gln Met Phe Ala Ile His Ser Leu Ser Gly  
100 105 110

Met Glu Ser Thr Val Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala  
115 120 125

Ile Cys His Pro Leu Arg His Ala Thr Val Leu Thr Leu Pro Arg Val  
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Thr Lys Ile Gly Val Ala Ala Val Val Arg Gly Ala Ala Leu Met Ala  
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Pro Leu Pro Val Phe Ile Lys Gln Leu Pro Phe Cys Arg Ser Asn Ile  
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180 185 190

Asp Asp Ile Arg Val Asn Val Val Tyr Gly Leu Ile Val Ile Ile Ser  
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Ala Ile Gly Leu Asp Ser Leu Leu Ile Ser Phe Ser Tyr Leu Leu Ile  
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Leu Lys Thr Val Leu Gly Leu Thr Arg Glu Ala Gln Ala Lys Ala Phe  
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Gly Thr Cys Val Ser His Val Cys Ala Val Phe Ile Phe Tyr Val Pro  
245 250 255

310

Phe Ile Gly Leu Ser Met Val His Arg Phe Ser Lys Arg Arg Asp Ser  
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&lt;210&gt; 778

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 778

Met Met Val Asp Pro Asn Gly Asn Glu Ser Ser Ala Thr Tyr Phe Ile  
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Leu Ile Gly Leu Pro Gly Leu Glu Glu Ala Gln Phe  
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&lt;210&gt; 779

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 779

Arg Thr Glu His Ser Leu His Glu Pro  
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&lt;210&gt; 780

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 780

Lys Met Leu Ala Ile Phe Trp Phe Asn Ser Thr Thr Ile Gln Phe Asp  
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&lt;210&gt; 781

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 781

Asp Arg Tyr Val Ala Ile Cys His Pro Leu Arg His Ala Thr Val Leu  
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Thr Leu Pro Arg  
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<213> Homo sapiens

<400> 782  
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Val Asn Val Val Tyr  
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&lt;400&gt; 786

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 <212> DNA  
 <213> Homo sapiens

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 <213> Homo sapiens

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&lt;210&gt; 789

&lt;211&gt; 492

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 789

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      35      40      45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
      50      55      60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
      65      70      75      80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
      85      90      95
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      100      105      110
Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
      115      120      125
Pro Ser Asp Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
      130      135      140
Glu Asn Arg Cys Val Arg Leu Tyr Gly Ser Asn Phe Ile Leu Gln Val
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Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp
      165      170      175
Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn
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Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser
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Glu Trp Ile Val Thr Ala Ala His Cys Val Glu Lys Pro Leu Asn Asn
      290      295      300
Pro Trp His Trp Thr Ala Phe Ala Gly Ile Leu Arg Gln Ser Phe Met
      305      310      315      320
Phe Tyr Gly Ala Gly Tyr Gln Val Glu Lys Val Ile Ser His Pro Asn
      325      330      335
Tyr Asp Ser Lys Thr Lys Asn Asn Asp Ile Ala Leu Met Lys Leu Gln
      340      345      350

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Lys Pro Leu Thr Phe Asn Asp Leu Val Lys Pro Val Cys Leu Pro Asn  
 355 360 365  
 Pro Gly Met Met Leu Gln Pro Glu Gln Leu Cys Trp Ile Ser Gly Trp  
 370 375 380  
 Gly Ala Thr Glu Glu Lys Gly Lys Thr Ser Glu Val Leu Asn Ala Ala  
 385 390 395 400  
 Lys Val Leu Leu Ile Glu Thr Gln Arg Cys Asn Ser Arg Tyr Val Tyr  
 405 410 415  
 Asp Asn Leu Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly  
 420 425 430  
 Asn Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser  
 435 440 445  
 Lys Asn Asn Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly  
 450 455 460  
 Cys Ala Lys Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe  
 465 470 475 480  
 Thr Asp Trp Ile Tyr Arg Gln Met Arg Ala Asp Gly  
 485 490

<210> 790  
 <211> 100  
 <212> PRT  
 <213> Homo sapiens

<400> 790  
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 Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val  
 20 25 30  
 Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro  
 35 40 45  
 Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val  
 50 55 60  
 Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys  
 65 70 75 80  
 Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val  
 85 90 95  
 Gly Ala Ala Leu  
 100

<210> 791  
 <211> 393  
 <212> PRT  
 <213> Homo sapiens

<400> 791  
 Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys Cys Ser Asn  
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 Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn Pro Ser Asn  
 20 25 30  
 Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp Glu Asn Arg  
 35 40 45  
 Cys Val Arg Leu Tyr Gly Ser Asn Phe Ile Leu Gln Val Tyr Ser Ser  
 50 55 60  
 Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Trp Asn Glu Asn  
 65 70 75 80

<213> Homo sapiens

BNSDOCID: <WO 0151633A2 | >

Leu Glu Lys Arg Glu Ala Glu Ala Met Val Leu Gly Ile Gly Pro Val  
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 Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp  
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 Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu  
 115 120 125  
 Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala  
 130 135 140  
 Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile  
 145 150 155 160  
 Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro  
 165 170 175  
 Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg  
 180 185 190  
 Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu  
 195 200 205  
 Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro  
 210 215 220  
 Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile  
 225 230 235 240  
 Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala  
 245 250 255  
 Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser  
 260 265 270  
 Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly  
 275 280 285  
 Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr  
 290 295 300  
 Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met  
 305 310 315 320  
 Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln  
 325 330 335  
 Gly Val Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp  
 340 345 350  
 Glu Gly Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile  
 355 360 365  
 Ser Leu Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly  
 370 375 380  
 Thr Arg Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala  
 385 390 395 400  
 Gly Ala Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala  
 405 410 415  
 Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr  
 420 425 430  
 Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr  
 435 440 445  
 Arg Gly Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser  
 450 455 460  
 Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val  
 465 470 475 480  
 Gly Ala Gly Gly Ser Gly Leu Leu Pro Pro Pro Ala Leu Cys Gly  
 485 490 495  
 Ala Ser Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr  
 500 505 510  
 Glu Ala Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile  
 515 520 525  
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met  
 530 535 540

Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser  
545 550 555 560  
Ala Ala Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val  
565 570 575  
Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala Gly Gly His His His  
580 585 590  
His His His  
595

